JANUARY 1951

The Review of Gastroenterology

OFFICIAL PUBLICATION

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

The Action of Drugs on the Human Biliary Tract

Enteric Cysts of the Stomach

Diaphragmatic Hernia

Infective Hepatitis

●

Sixteenth Annual Convention
Chicago, Ill., 17, 18, 19 September 1951

VOLUME 18 NUMBER 1

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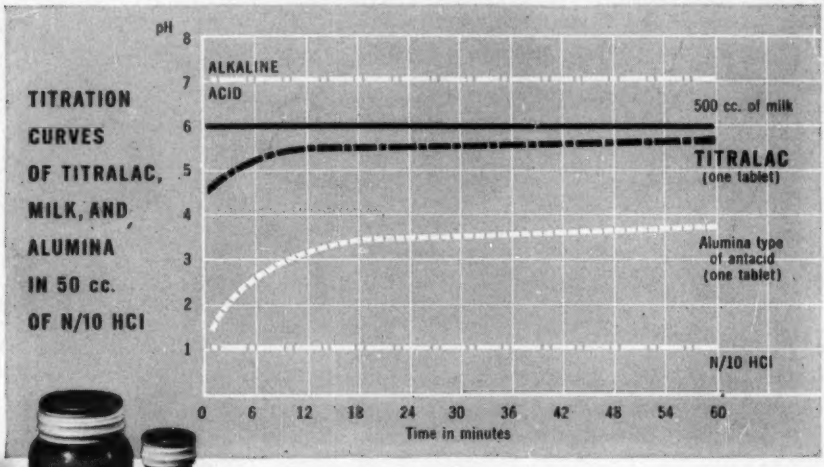

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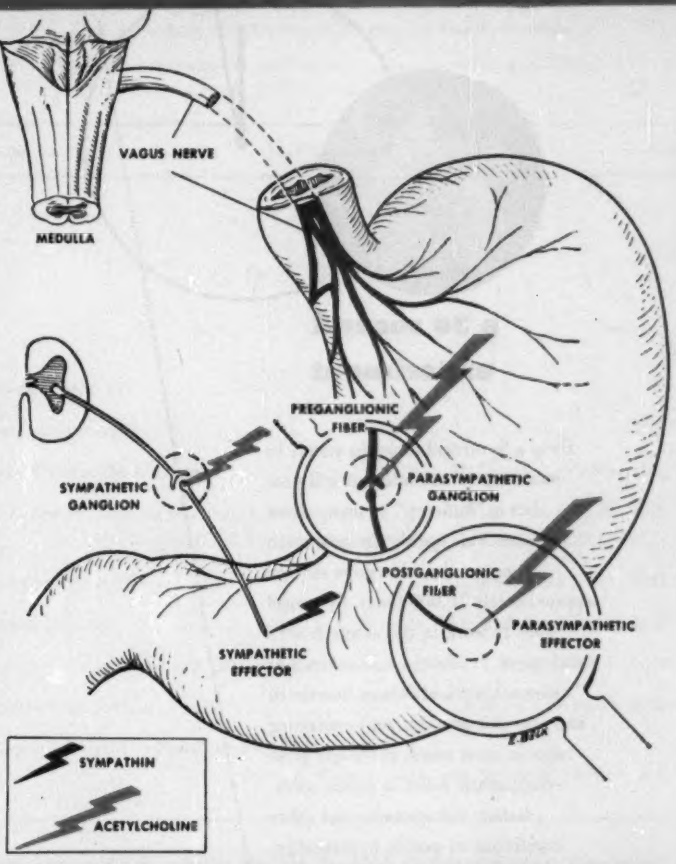

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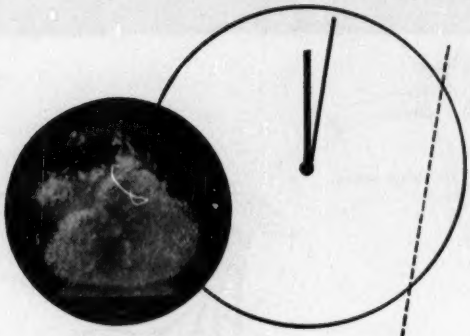

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The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

VOLUME 18 JANUARY, 1951 NUMBER 1

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of the

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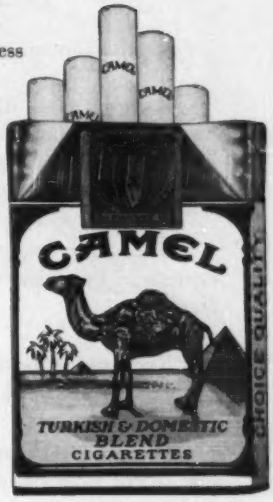

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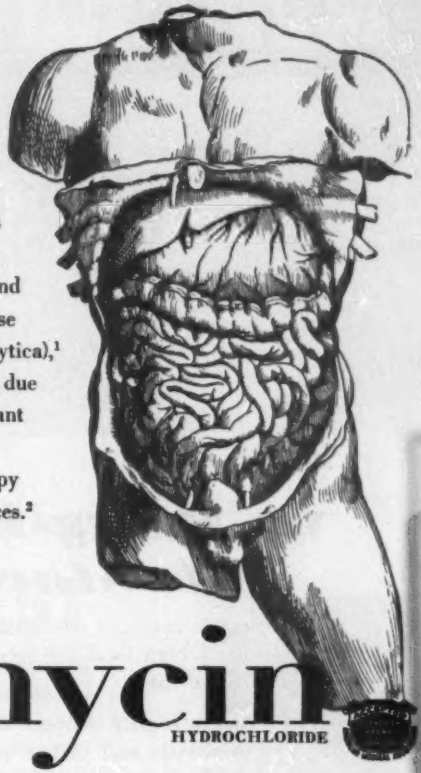

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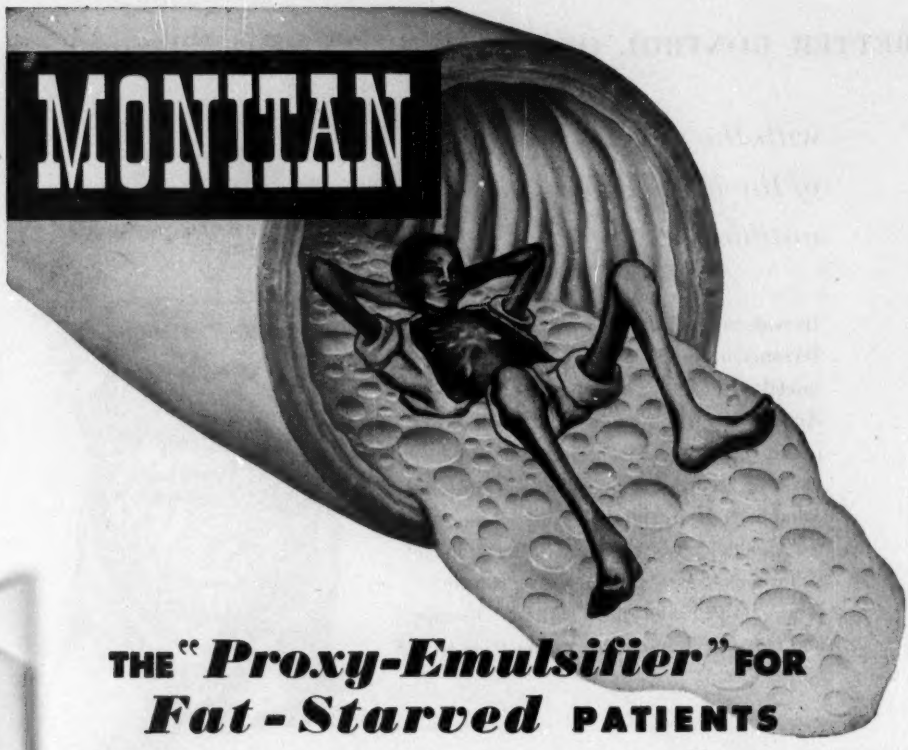

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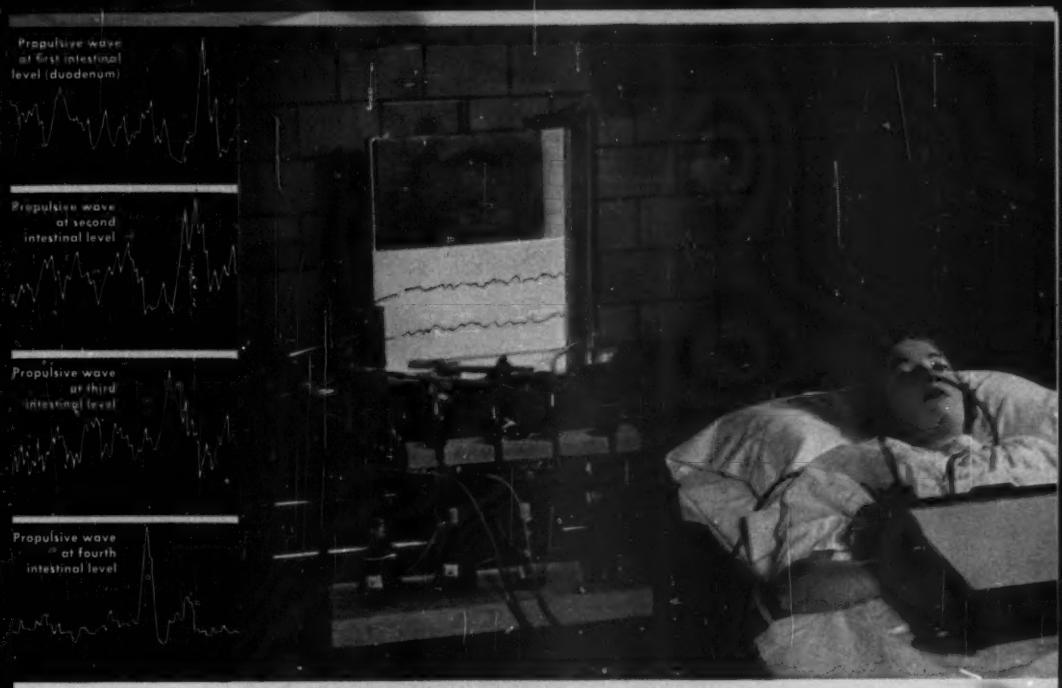
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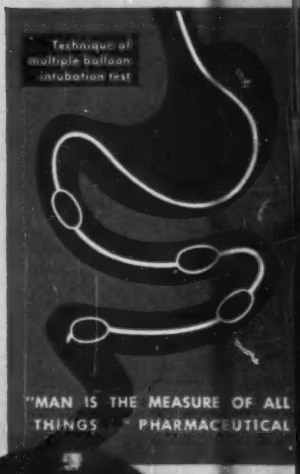

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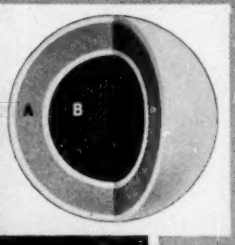

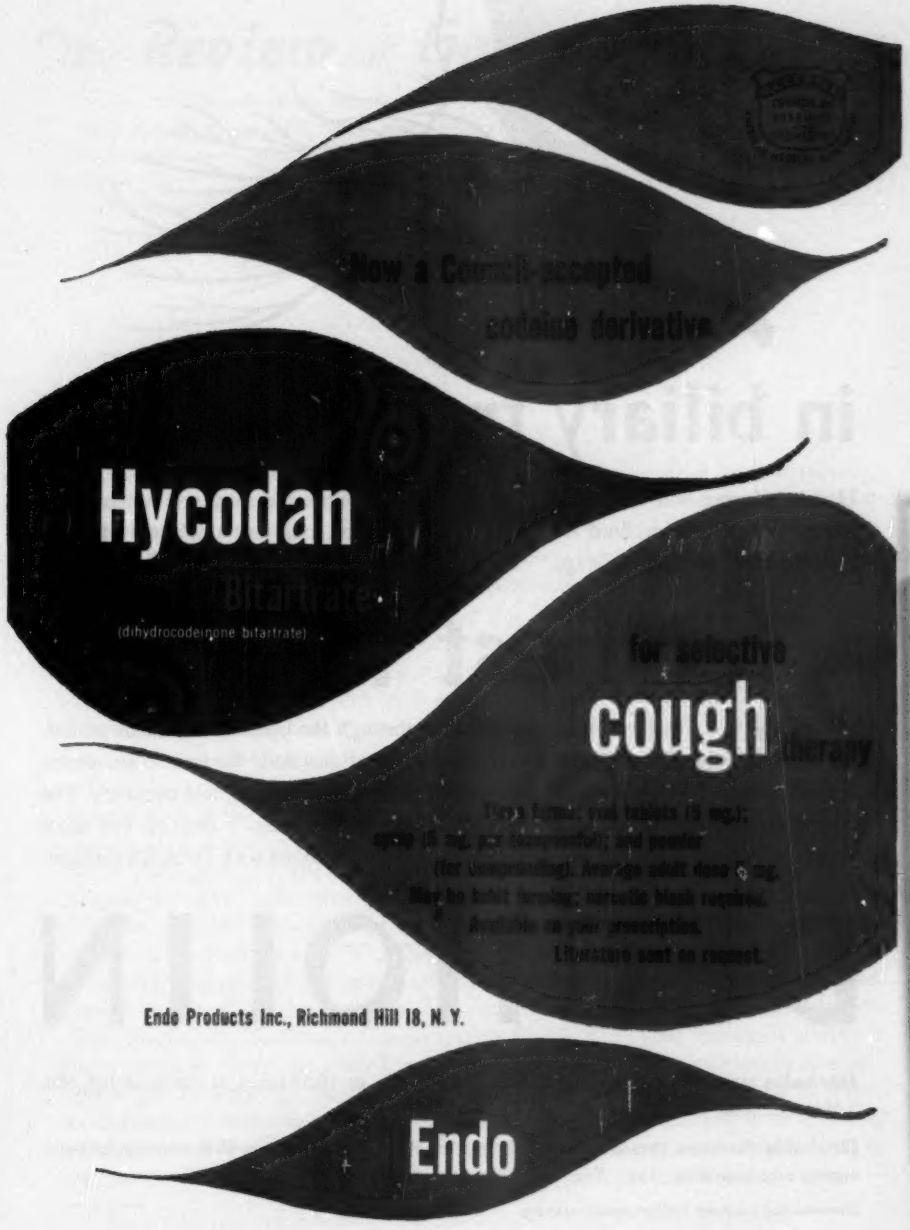

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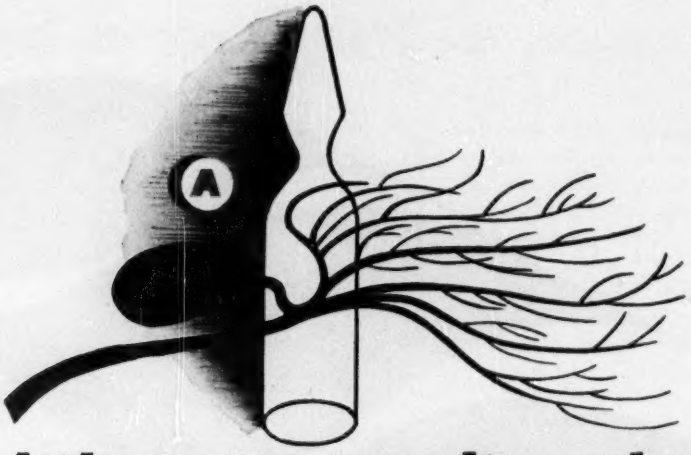

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Volume 18 JANUARY, 1951 Number 1

ENTERIC CYSTS OF THE STOMACH*

A Case Report

GORDON McNEER, M.D.

and

L. J. SPITZ, M.D.

New York, N. Y.

The rarity of enterogenous cysts is well known. In reviewing hospital records, Mayer[21] failed to encounter a single example of such lesions in the course of 80,000 postmortem examinations. Though numerous reports of intestinal enterogenous cysts may be found in a study of the medical literature, only six instances of this entity have been described as arising in the stomach.

While known to occur at any level of the oro-esophago-gastrointestinal tract, the most frequent site of involvement is the ileocecal junction. Kettle[16] reported eighty-eight case histories of which seventy-one were found in the small intestine, and seventeen in the colon. Yet, they may likewise occur in the duodenum[4,26], mediastinum[35] and at the base of the tongue[32].

Enterogenous cysts may be classified as submucosal, intramuscular, subserosal, or intramesenteric. More frequently, however, these lesions are closely attached to some portion of the alimentary tract. They are generally hollow structures possessing a wall of smooth muscle (usually two layers) and a mucosa. An important feature is that, generally, the muscle coats are closely allied to, and at times, are an integral part of the muscularis of the intestinal tract. The epithelium of enteric cysts need not resemble that of the adjacent structure, but may be similar to any other portion of the digestive tract[32,33]. The epithelial layer of the cyst may be altered by intracystic pressure with resulting atrophy; through inflammatory changes; and through action of the digestive enzymes secreted by the cells themselves. Identification has thereby been made difficult and confusing. The cystic content is usually a thin or mucoid glairy material. The only report of chemically analyzed fluid available is that of Basman[1]. He described the case of a four weeks' old child in whom a duodenal cyst was encountered. Upon analysis the fluid was found to be alkaline, possessing a carbon dioxide content of 54.5 volume per cent, and entirely free of amylase.

*From the Strang Cancer Detection Clinic and Gastric Service of Memorial Hospital.

The embryonic origin of these structures is debatable. Lewis and Thyng[18] found, in dissecting the esophagus, stomach, and intestines of rabbit, pig, and human embryos, regularly occurring nodules of epithelial cells. In following the course of development these investigators found that they became vacuolated; either breaking off from the lumen of the intestinal tract, or remaining in continuity with the lumen. Though more commonly disappearing, some were found to persist or become fused with the lumen of the digestive canal. Embryologically, this seems to be the explanation of the widely separated enteric cyst of the intestinal tract. Following Thyng and Lewis' explanation, Ladd[17] postulated the "pinching off" of the diverticula of the fetal intestinal tract to form cysts. Ewing[9] believed these lesions represent embryonic rests similar to dermoid cysts. Those diverticular cysts arising in the region of the ileocecal juncture are thought to be from the omphalomesenteric duct, or its remnant. Of these, Meckel's diverticulum is the most frequent occurring example. When enterocystomas communicate with the intestinal lumen their origin is considered to be from a fetal diverticulum. Ladd and Gross[17], Sherwin[32], and others[26] refer to this type of enteric cyst as "reduplication" of the intestinal tract.

Enteric cysts of the stomach are found generally in infants corresponding with enterocystomas found elsewhere in the intestinal tract. These tumors are found early in life, primarily because of their size, and the position occupied. The symptoms may be obstructive in nature but as in the case of Cabot[6] unexplained cyclic vomiting may bring the child to medical care. Also, failure to gain weight may be a presenting symptom in the younger age groups. The older the patient, the more difficulty is experienced in reaching a preoperative diagnosis. After a most careful radiographic and clinical study, our patient was thought to possess a cyst arising from the head or body of the pancreas. A vague sense of fullness after meals, hematemesis, or symptoms suggestive of peptic ulcer may indicate an enteric cyst of the stomach. Though a mass may be more readily palpated in the younger age groups, physical examination is generally noncontributory in the older subjects. Routine laboratory studies offer little assistance. A carefully conducted x-ray examination of the gastrointestinal tract may disclose a widened duodenal loop, displacement of the stomach, or a definite tumor.

Though more frequently encountered on the greater curvature side of the pylorus, enteric cysts of the stomach may arise in any layer or part of that organ. After a careful search of the literature, the authors have found only six case reports of such lesions since 1916. Lyons[19] reported a cyst lying along the greater curvature of the stomach in a nineteen (19) day old infant. It measured 3½ x 2½ inches, and extended beyond the greater curvature. Microscopically, the structure was similar to that of the stomach, except that the mucosa was thinner. Ladd and Gross[17] described two additional examples; one in an infant of two months, and the other in a child of nine years. In Ferrara's[10] case, there was no communication existing between the stomach and the cystic structure. Cabot[6] found a plum-shaped tumor in the stomach of a seven-year old child. Although arising from the pylorus it was

adherent to the transverse mesocolon. The mucosa was microscopically found to be atrophic, but gastrointestinal in character. Wendel[36] discovered, in operating on a thirty-year old woman, a large cyst of the gastric antrum on the greater curvature. This process did not communicate with the lumen of the stomach, and microscopically possessed a well differentiated mucosa, submucosa, and muscularis.

Treatment

Surgical intervention is invariably indicated. Whereas excision may appear feasible for the extraluminal cysts, partial gastrectomy is otherwise advisable. Enucleation would leave a very poor functioning gastric segment. If the process

Fig. 1—X-ray film demonstrating deformity produced by extrinsic pressure on gastric antrum and duodenum.

were obstructing the pylorus of an infant, a rapidly performed anterior gastroenterostomy might be more advisable, with the idea of resecting the lesion at a later date.

The case history of a 34-year old male found to have an enterogenous gastric cyst during laparotomy at Memorial Hospital is worthy of interest.

T. F., a white male age 34, appeared at the Strang Cancer Prevention Clinic on April 10, 1947. His history dates back to 1936 with the onset of an intermittent epigastric pain, centrally located, relieved by the ingestion of food. Within three or four weeks a 15 pound weight loss and tarry stools were noted. At no time was there nausea, vomiting or diarrhea. A gastrointestinal x-ray series allegedly demonstrated a duodenal ulcer. Prompt relief of symptoms was obtained by a dietary regimen. Some three months later following indiscretions, symptoms returned. However, with

strict adherence to his "ulcer regimen" T. F. remained symptom-free for a period of eight years.

In 1944, at the site of the pain previously experienced, there was noted a sense of pressure, which was limited to a "finger point" area in the mid epigastrium. The pressing sensation was intermittent with periods of remission lasting five to six weeks. No relief was obtained with return to the previously successful dietary management. Concomitantly there occurred a "sense of bloating after a normal sized meal". Whereas the epigastric pressure was intermittent, the sense of fullness persisted and worsened, and it was this latter complaint which eventually forced the patient to seek relief.

Physical examination revealed no abnormal findings. Laboratory studies were as follows: Hemoglobin 97 per cent, W.B.C. 5,400, 65 per cent polymorphonuclear leucocytes, 1 monocyte, 34 per cent lymphocytes. Mazzini test was negative; urinalysis normal. Serum bilirubin was 1.3 mg./100 c.c., serum calcium 12.4 mg./100

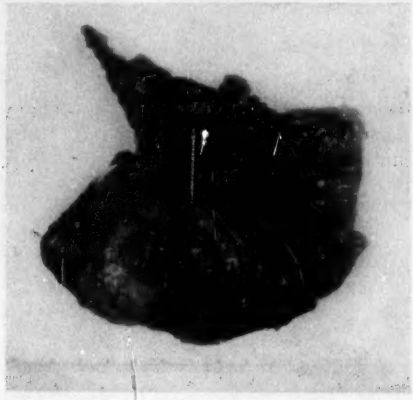

Fig. 2—Photograph of gross specimen demonstrating lining and inner surface of enterogenous gastric cyst.

c.c.; serum chlorides 99 milliequivalents; alkaline phosphatase 3.6 units/100 c.c.; inorganic phosphorus 3.26 mg./100 c.c.; serum proteins 7.4 gm./100 c.c.; blood sugar 87 mg./100 c.c. Urea nitrogen 12.3 mg./100 c.c. Cephalin flocculation negative in 24 hours, 3 to 4 plus in 48 hours. Stools were negative for blood on repeated examination. Duodenal contents were positive for traces of amylase but negative for bile crystals or blood.

X-ray examination of the upper gastrointestinal tract on several occasions demonstrated the stomach to be displaced slightly to the left and anteriorly. The duodenal loop was widened and deformed (see Fig. 1). This suggested the possibility of a pancreatic cyst. Barium enema and cholecystograms were negative.

At laparotomy the distal-third of the stomach was found to be occupied by a cystic fluctuant structure measuring seven cm. in diameter. The liver appeared normal; there were no palpable lymph nodes; the peritoneal surface was smooth, shiny

and glistening. The mass was removed in toto by partial gastrectomy, without postoperative complication.

Pathologically the specimen consisted of a portion of stomach removed by partial gastrectomy. The proximal line of excision was in the mid portion of the stomach, the distal line of excision lay proximal to the pylorus. The specimen measured 9 x 8 x 4 cm. An oval tumor occupied the entire greater curvature of the surgical specimen. Upon opening the stomach, the mucosa was found intact. The tumor proved to be an intramural cyst situated in the wall of the greater curvature, and in no way connected to the gastric mucosa. The cystic content was a clear, serosanguinous fluid. The wall of the cyst was yellowish white and fibrous in appearance, possessing several small granular polypoid lesions measuring 2-3 mm. The cystic cavity measured 5 x 5.5 cm.

Histology

The wall of the cyst is composed of the same number of layers as is the stomach proper; namely, mucosa, submucosa, muscularis and serosa. The mucosa for the most part is made up of a single layer of tall columnar epithelium with basal nuclei and acidophilic cytoplasm. In several areas, mucus is present in the cytoplasm, and in a few small patches the mucosa is thickened by glands resembling pyloric glands. There is a loose subepithelial infiltration of lipoid histiocytes and lymphocytes; the latter are occasionally clustered in masses. The muscularis mucosa is especially prominent. The submucosa is edematous and also infiltrated with lymphocytes. The muscularis comprises a circular, longitudinal and oblique layer, quite often the pattern of the corresponding layers of the stomach. The serosa is not noteworthy.

Conclusion

The great rarity of this lesion warrants the inclusion of this case report in the medical literature.

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Beschreibung eines Operative Entfernren Congenitalen Nebenmagen. Arch. f. klin. Chir. **95**:895-898, 1911.

THE ACTION OF DRUGS ON THE HUMAN BILIARY TRACT*

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This paper represents a brief resumé and review of action of drugs commonly used in the treatment of biliary disease. No attempt is made to include all the drugs used nor to cover the literature in its entirety. In the first part of the review, the drugs are divided according to the part of the biliary tract upon which they exert their action, such as, the biliary tree proper, the gallbladder and the sphincter of Oddi. The second part deals with the use of drugs in various clinical manifestations of biliary disease.

A. Biliary Tree

1. *Choleretics:*—(a) *Bile Acids:*—Berman, Snapp, Ivy, Atkinson and Hough[1] showed that the oxidized, unconjugated bile acids such as dihydrocholic acid and ketocholanic acid produced an increase in the volume of bile because of a greater water content, whereas the whole ox-bile produced an increase in all the constituents of bile. Dolkart[2] found that the oxidized bile acids were much better tolerated than the unoxidized type given in the form of dried ox-bile. Brown and Dolkart[3] also recommend ketocholanic acid as an effective type of choleretic. Sixty-five patients were studied. In some cases, stones visible on the first x-rays were not seen after therapy. Even patients who gave a history of frequent repeated attacks of gallbladder colic obtained gradual disappearance of symptoms under treatment. They recommend frequent feedings with cream, associated with ketochlanic acids and antispasmodics. This treatment is contraindicated in the presence of common duct obstruction or acute cholecystitis. Teeter[4] showed that patients given bile salts following cholecystectomy were able to tolerate a full diet much more quickly than a control group. He recommended administration of bile salts, either before or with meals. Best[5] found that bile acids increased the intrabiliary pressure.

(b) *Secretin:*—Grossman et al[6] found that secretin stimulates the secretion of bile in man as in other species. The increase in volume is associated with decrease in concentration of bilirubin and cholic acids and in viscosity, indicating that secretin increases only the water content; thus, it may be classified as a hydrocholeretic.

Comment:—The beneficial effects attributed to the administration of choleretics in biliary disease may be due to several factors:

(1) *The hydrocholeretic action,* producing an increase in the flow of bile and an increase in the water content, may act beneficially in washing out bacteria from the higher radicles of the biliary tree. This would be beneficial only if the bile had free access into the duodenum, there being complete absence of spasm, or in the

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case in which an indwelling T-tube is in the bile duct itself. If there is any impediment to the flow of bile from conditions such as duodenal spasm, ampulla edema, or pressure from the head of the pancreas, then the increased intrabiliary pressure from bile salts could presumably add to the discomfort of the patient. To eliminate duodenal spasm, one should at the same time administer nitroglycerin.

(2) *Relief of constipation:*—Those of us who see a great deal of biliary tract disease are impressed with the symptomatic relief obtained from proper evacuation of the bowels. Many of the commercial bile salt preparations contain a laxative as well, and probably a great deal of benefit has been due to this action. Ivy and Goldman[7] in experimenting with dogs showed that constipation or obstruction of the colon or stimulation of various branches of the splanchnic nerves may predispose to stasis of the biliary tract, by decreasing bile formation and by increasing the resistance to the flow of bile through the sphincter of Oddi into the duodenum.

(3) *Sedative action:*—As is pointed out elsewhere in this paper, the administration of sedatives is extremely helpful in biliary disease, particularly when there is a great deal of duodenal spasm. Here again, many of the commercial bile salt preparations contain sedatives and probably a great deal of benefit obtained may be attributed to their action. Frequently, in studying the intrabiliary pressure in patients postoperatively, we have been impressed with the fact that if the patient is unduly nervous, the pressure in the common bile duct will be elevated. This is due to the spasm of the duodenum. This passes off within a few minutes after the patient becomes more relaxed.

2. *Chemotherapy and Antibiotics:*—Morrison et al[8] reviewed the literature with reference to the infection theory of gallbladder disease. Those who accept the infection theory are divided between those who believe the streptococcus to be the chief offending organism and those who contend that the bacillus coli plays the chief role. Others claim that infection plays no role at all in gallbladder disease. These investigators[8] took cultures from the submucosa of the gallbladder wall and cystic duct in over 20 cases. In the cases where there was no empyema, the cultures from the gallbladder wall were sterile. In two cases of empyema of the gallbladder a pure culture of E. coli was found in one and hemolytic streptococcus in the other. In a second series of cases, they obtained bile from duodenal drainage in the following manner: A duodenal tube which was encased in a second gelatin tube was passed. The gelatin tube dissolved after it passed into the duodenum so that specimens could be taken for culture. Two hundred and forty-four cases were studied, in 12 of which the streptococcus was found. In 10 of these 12 cases, the bacteria disappeared from the duodenal drainage fluid on sulfonamide therapy, and the patients' symptoms were relieved.

Giardia lamblia has been proven to cause infection of the biliary tract in a small number of cases. Burroughs, Nussbaum and one of us[9] (McGowan) reviewed the literature on the subject and recently reported a proven case. There is evidence that this protozoon is present in the biliary tract more often than is generally supposed. When present the organism may be recovered by duodenal drainage. Quinacrine is a specific treatment for this condition.

Shay, Komarov, and Siplet[10] found in normal dogs that sulfathiazole, sulfasuxidine and sulfathalidine were concentrated in the gallbladder in direct proportion to the amount of water absorbed from the bile.

Zaslow, Counseller and Heilman[11] found that streptomycin and penicillin were excreted in adequate concentrations in the hepatic bile of patients with T-tubes, in whom there was little or no liver damage. In the presence of jaundice, as would be expected, the ability of the liver to excrete antibiotics is impaired. In cases with long persistent obstructive jaundice, no antibiotic agent was excreted in the bile. As the level of serum bilirubin falls, following relief of obstruction of the common duct, more and more of the antibiotic agent is excreted in the bile. The conclusions from these studies are that the mechanical agents producing obstruction to the flow of bile must first be surgically removed before a great deal of benefit can be obtained from antibiotics.

Hewlett and Ernstene[12] reported a case of brucellosis due to *Brucella abortus* in which the organism was cultured from bile obtained by duodenal drainage. They treated the patient with streptomycin intramuscularly in doses of 0.5 gm. every three hours for a total of 28 gm. As a result of this treatment, the cultures from bile obtained on duodenal drainage became sterile. They attributed their success to the fact that the organisms in the gallbladder are subject to higher concentrations of streptomycin than in other tissues.

Rehfuss[13] made an exhaustive study into the etiology of gallbladder disease. He classified the various theories of etiology as: (1) infections; (2) alteration of gallbladder contents (bile salts); (3) reflux of pancreatic juices; and (4) toxin dissemination. He was able to produce experimental cholecystitis in 22 per cent of dogs in his early series and was able to increase this incidence to 68 per cent in a later series. This was accomplished by the use of a single antigen, nonhemolytic streptococcus, in nearly 700 animals. Repeated injections over a period of months resulted in a marked increase in the incidence of lesions. The antigen, however, produced side-effects such as reactions in the joints. It is his conclusion that cholecystitis is due to mild repeated infection acting slowly on the different parts of the gallbladder wall.

3. *Methods and Agents Supposed to Dissolve or Aid in Passing of Common Duct Stones:*—In 1935, Pribram[14] described a method for treatment of common duct stones in poor risk cases. At operation he passed a T-tube through the cystic duct into the common bile duct. Subsequently he instilled one to three cubic centimeters of ether into the bile duct repeatedly in hopes of dissolving or fragmenting the stones. Walters and Wesson[15] reported a case in which they injected 5 c.c. of ethyl ether into the common bile duct through a T-tube on several occasions and on other occasions 10 c.c. of equal parts of alcohol and ether. Following one of these injections the patient experienced an attack of severe pain for which amyl nitrite was administered with complete relief. On subsequent cholangiograms a common duct stone which had previously been present was no longer seen. Vayo[16] used a mixture of one part alcohol and two parts ether. He injected 5 c.c. of this solution into the common duct with the hopes of fragmenting the stone. He warned

against repeated use of this treatment because of the possibility of producing liver damage. Best[5] instituted the biliary flush method of eliminating stones from the common bile duct. He administered bile salts to raise the intrabiliary pressure. He also used repeated irrigations of the bile duct together with instillation of olive oil. Combined with this he used antispasmodics such as nitroglycerin and atropine to relax the spasm of the sphincter of Oddi.

Comment:—The instillation of ether into the common bile duct must be done with exceeding care. Ether boils at body temperature and if the injection is continued, very high pressures will develop in the common duct. It is probably these high pressures, as a result of the ether vapor, that have been instrumental in forcing the stones through the ampulla of Vater, rather than the dissolving effect of the solution. It is probable that very few stones have actually been dissolved or fragmented by ether, since one can frequently place stones from a gallbladder in ether for many days without very much going into solution. The only proof that we have that stones are actually fragmented is x-ray evidence which may often be inaccurate in the interpretation of the size and shape of these small objects. The high pressures developed within the duct frequently result in an attack of cholangitis. We have seen several severe attacks with temperature elevations up to 105° F. following such procedures. We have personally known of two cases in which stones were passed following administration of amyl nitrite alone. In each case the tube was clamped off until severe pain developed, indicating a good head of pressure behind the stone. Four inhalations of amyl nitrite were then taken, following which the patients had complete relief of pain. Subsequent x-rays showed the stones to be absent.

We have used the following method at the Boston City Hospital for the purpose of encouraging common duct stones to pass. A saline bottle is connected to the T-tube. A pressure manometer is also connected to the system through the medium of a Y-tube. The patient's pain level is determined. Water is then perfused into the common duct continuously under pressure, less than the previously determined pain level. Periodically the patient is given inhalations of amyl nitrite. Concurrently with this treatment, mineral oil is sometimes injected into the common duct in order to permit the stone to seal off the lower end of the common bile duct and thus cause a head of pressure behind it. Periodically, ether is instilled into the common duct in doses of about 5 c.c., care being taken not to permit the ether to develop high pressures. If the patient complains of pain during injection, the syringe is immediately disconnected and the T-tube allowed to drain. We have successfully caused seven stones to be passed in one patient, and have washed out one to two stones from the common duct in each of six other cases by this method. There have been four other cases in which the method was a failure, in which ether and irrigations failed to eliminate the stone after many periods of trial. Two required subsequent surgery and two have remained entirely well without the need of further surgery for ten and two years, respectively. It is recommended that if these methods fail and if the stones still persist but are small and if the biliary dynamics return to normal, that is, the resting pressure

level is less than 30 mm. of water above the ensiform and the pain level is greater than 500 mm. of water, then the T-tube should be removed[27]. The patients then will remain symptom-free for an indefinite period of time. In this way, it is our belief, many patients will be saved further operation. If, on the other hand, the biliary dynamics do not return to normal, then one should operate while the tube is still in the bile duct.

4. *Cholangiography:*—We have found Diodrast to be the best material for cholangiography. It is used in a 30 per cent solution injected directly into the T-tube by the following methods: As much bile as possible is aspirated through the tube with a syringe. One must exercise great care in preventing air bubbles from getting into the T-tube, since they will produce artefacts on the x-ray film which simulate stones. These air bubbles may remain in the common duct for several days, so that x-ray should be repeated after an interval of a week in order to be sure that the shadows seen are actually stones. Besides the presence of stones, the cholangiogram will frequently demonstrate pancreatitis, stricture or spasm. After aspirating the bile, a second syringe containing 20 c.c. of Diodrast is applied to the T-tube. The Diodrast is then injected slowly until 10 c.c. have been injected or until the patient complains of pain, whichever comes first. Then the physician injecting the opaque fluid asks the patient to hold his breath. This is the signal for the x-ray technician to make the exposure. The patient is then given 11.0 mg. of morphine sulfate to produce a spasm of the second portion of the duodenum and 10 minutes later a second x-ray film is taken, after the injection of Diodrast as previously described. The spasm from the morphine will force the Diodrast up into the smaller radicles of the biliary tract. Following this second picture, the patient is given four inhalations of an 0.3 c.c. pearl of amyl nitrite, 10 c.c. of Diodrast are again injected and a third picture is taken. In this way, one can obtain films of the biliary tree in various states of function: (1) in the resting condition; (2) following the spasm from morphine, in which the opaque media is pushed up into the small radicles of the biliary tree; and (3) following the inhalation of amyl nitrite, in which the duodenum will be entirely relaxed and medium will flow freely into the duodenum unless prevented by stricture, stone or edema.

B. Gallbladder Proper

Higgins et al[17] studied the effect of drugs in the isolated gallbladder of the dog and guinea pig and found that histamine produced contraction but abolished rhythm; atropine produced relaxation; pilocarpine, on the other hand, produced contraction, and strophanthin increased the tonic contraction but abolished rhythmic activity. Dolkart[2] recommended the use of eggs, cream and butter in gallbladder disease for the purpose of facilitating emptying. Schube, Myerson and Lambert[18] showed by the use of x-ray studies that Mecholyl has practically no effect on the size and shape of the gallbladder, but this drug in the majority of cases definitely inhibits the emptying of the gallbladder following the ingestion of a fatty meal. Doubilet and Ivy[19] studied the action of cholecystokinin on humans and dogs. They noted that if the gallbladder was under initial pressure, the drug had very little action. Three to four hundred mm. of water pressure in the gall-

bladder for a two-hour period definitely diminished the action of cholecystokinin. This phenomenon is true in all muscular organs, that is, if the muscle is overstretched it is at a tremendous mechanical disadvantage.

Comment:—Cream taken when the stomach is empty, usually just before going to bed, is an excellent stimulus to promote emptying of the gallbladder. Its regular use in gallbladder disease should not be instituted until the patency of the cystic duct has been determined by x-ray. It is also inadvisable to stimulate gallbladder emptying in the presence of small stones since this would encourage passage into the common bile followed by biliary obstruction and jaundice.

C. Sphincter of Oddi and Musculature of the Duodenal Wall

1. *Spasmogenic Drugs:*—Butsch, Walters and one of us[20] (McGowan), by measuring the pressure in the common bile duct in patients with indwelling T-tubes, developed a method for studying the action of various drugs on the sphincter of Oddi in the human. It was found that morphine produced marked spasm of the sphincter of Oddi demonstrable by an increase in intrabiliary pressure. This increase in pressure reached levels as high as 350 mm. of water and produced in some individuals biliary pain similar to that suffered prior to operation. It was also found that this spasm could be readily relaxed by four inhalations of amyl nitrite or sublingual administration of glyceryl trinitrate in doses of 0.43 mg. Subsequently, it was determined that the spasm produced my morphine occurred in the whole second portion of the duodenum[21]. In addition to morphine, it has been found[22] that Pantopon, 21.6 mg.; Dilaudid, 2.0 mg. and codeine, 65.0 mg., all produce similar duodenal spasm but to a lesser degree. Demerol[23] was also found to produce a variable degree of duodenal spasm in occasional cases, as much as did morphine, but in most cases considerably less.

2. *Spasmolytic Drugs:*—Drugs found to produce marked relaxation of the second portion of the duodenum and sphincter of Oddi are: Amyl nitrite, with the effect lasting approximately three minutes; nitroglycerin, 0.25 mg. to 0.65 mg., the effect lasting for approximately one hour, and intravenous aminophylline with the effect lasting from five to fifteen minutes. Drugs having no spasmolytic action on the second portion of the duodenum include: Atropine, 0.8 mg.; hyoscine hydrobromide, 0.65 mg.; adenosine phosphoric acid, 40 mg.; 30 c.c. of ethyl alcohol; 0.6 mg. of histamine; 50.0 mg. of ephedrine and 1 c.c. of 1:1000 solution of epinephrine. Intravenous administrations of 10 c.c. of a 10 per cent solution of calcium chloride also failed to produce any relaxation of the sphincter of Oddi, as did a 32.0 mg. of papaverine hydrochloride. Parasympathomimetic drugs such as neostigmine and acetylcholine were also without effect. Five-tenths c.c. of a 1:2000 solution of ergotamine tartrate, 500.0 mg. of caffeine and 130.0 mg. of phenobarbital sodium produced no effect.

Comment:—The parasympathomimetic drugs such as tincture of belladonna, atropine, hyoscine and their derivatives have been frequently found to be beneficial in gallbladder disease, particularly if there is a complicating pancreatic edema. The beneficial effect noticed is probably due to a decreased effect of vagal impulses and a reduction in the amount of pancreatic juice that is released.

D. Pain-Relieving Agents

Morphine sulfate has been found to relieve biliary pain more effectively than an equivalent dose of one of its derivatives[24]. However, the spasm produced by morphine, together with the nausea it causes, sometimes adds greatly to the discomfort of the patient. The derivatives such as Dilaudid, Pantopon, Demerol and codeine[22,23] all produce duodenal spasm to a variable degree. They do not, however, tend to produce as much nausea as does morphine. On the other hand, a specfic drug which produces a great deal of discomfort in one patient may be well tolerated by another. No set rule can be made as to which is the best drug in any individual case.

In this review we have confined our discussion to drugs that act directly on the biliary tract and have made no attempt to cover all forms of therapy used in the treatment of gallbladder disease and in the treatment of complications and side reactions, such as Vitamin K for the control of hypoprothrombinemia; phenobarbital for the control of nervousness; vitamin therapy, particularly B and C for the purpose of promoting wound healing and for correcting the deficiencies produced by the disease; atropine derivatives for controlling recurrent pancreatic edema, a complication of biliary disease; a high carbohydrate, high protein diet to support the liver which is often damaged in these conditions; special diet and liver extract for the control of gastritis, another complication; and lastly, a proper regimen combined with the right type of laxative for the regulation of bowel habits so necessary for the medical management of biliary tract disease.

E. Clinical Application

1. *Chronic Cholecystitis with Adequate Function and Without Stones:*—Chronic cholecystitis, particularly in the young female, in which the gallbladder fills and empties, will frequently respond to medical treatment[25]. Indeed, it is in this type of gallbladder disease that the results of surgery are very frequently disappointing. The treatment should be aimed at relaxation of the sphincter of Oddi to permit bile to flow freely into the duodenum, in this way decompressing the biliary tract and intermittently emptying of the gallbladder. In general, the patient may eat a well-balanced diet including cream and butter, plenty of protein, particularly meat, fish, cheese and milk, and carbohydrate in the form of starchy foods, sweets and hard candy. Spices, chocolates, pickles, fried foods, gravy and cooked fats, especially those cooked with vegetable fats, should be avoided. Nitroglycerin in doses of 0.25 mg. to 0.65 mg. should be taken under the tongue every three hours for several days in order to decompress completely the biliary tract. The patient should take up to half a glass of coffee cream every night at bedtime when the stomach is empty. This will promote emptying of the gallbladder. This treatment may at first make the patient very nauseated and she may vomit bile. This is due to the fact that, for a long period prior to treatment, the gallbladder had not properly emptied, so that with the initiation of the proper regimen, the concentrated bile in the gallbladder passes into the duodenum. It then is regurgitated into the stomach where it induces symptoms of nausea and vomiting. Later

on, as the biliary tract is thoroughly decompressed and the gallbladder fills with fresh clean bile, the symptoms will gradually improve. The patient should be warned about these initial symptoms. The following is a list of instructions that is given to the patient to be followed along with the administration of nitroglycerin:

1. Crush the tablet between the teeth and roll the fragments under the tongue and remain lying with three pillows under the head for ten minutes. 2. A flushing of the face and a throbbing sensation in the head should follow the taking of each tablet. If this does not occur, a fresh supply should be obtained or the dosage may be increased to two tablets. 3. The tablets may produce nausea and at times vomiting of bile, in a few cases. While this is not necessary to the success of the treatment, it is a good sign. Vomiting should disappear after a few doses. 4. When this medicine is being kept for emergency use, it should be tested for freshness about every three weeks by taking a tablet in the above manner. 5. The action of this medicine is to relax muscle spasm and allow the bile to flow freely from the liver into the intestinal canal. 6. If pain or indigestion does not improve in spite of treatment, then the condition is probably one which this treatment will not help and other measures will be required. 7. If headache is prolonged or excessive, you may discontinue the medicine until you have further instructions. 8. Take one-half glass of coffee cream every night at bed time. 9. Eat a well-balanced diet especially meat, fish, cheese and milk; starchy foods, such as potatoes, bread and vegetables; sweets, such as hard candy and rich desserts. 10. Avoid spices, chocolates, pickles, fried foods and gravy; fatty foods, especially those made with vegetable fats such as Crisco. Cream and butter are permissible.

After three or four days of nitroglycerin therapy, the patient may then be given nitroglycerin three times a day after meals and at bedtime for a further three-week period, at the end of which time, if she is symptom-free, the treatment may be discontinued. However, she should be instructed that at any future time that symptoms develop she should freely take nitroglycerin. In addition, she should continue to take cream twice a week on an empty stomach in order to permit periodic emptying of the gallbladder. We have used this treatment over the past ten years with a fair degree of success. However, there are some cases in which treatment is of no benefit. In these instances, even if the x-ray of the gallbladder is negative for evidence of disease, operation has been advised; in a surprisingly large number of cases, stones were found which did not previously show up in the x-ray.

2. *Chronic Cholecystitis Without Function or With Stones:*—In the case with nonfilling of the gallbladder after repeated x-rays, or with definite proven stones, surgery should be advised, even if the symptoms are only slight. However, if the patient is asymptomatic or if the symptoms are relatively slight and there is a contraindication to surgery, such as coronary heart disease, hypertension or old age, then the above medical regimen may be tried, as far as the nitroglycerin therapy is concerned. The cream, however, is omitted on the basis that if the gallbladder is not functioning, there is no point in encouraging it to contract; harm might possibly result. We have used this regimen in a considerable number of

cases in which stones were present, even in the common bile duct, with excellent results. However, in another similar series of cases in which severe symptoms continued, surgery was advised. Gallbladder surgery, when necessary to relieve suffering, even in the presence of unfavorable conditions such as those mentioned above, is fairly safe and it is remarkable how well some of these patients do after cholecystectomy.

3. *Biliary colic:*—The patient suffering from an acute attack of biliary colic, rolling around for many hours complaining of severe right upper quadrant or mid-epigastric pain radiating into either scapular region or into the subpectoral region or even down in the right lower quadrant of the abdomen, frequently presents a problem. If the pain is due entirely to duodenal spasm with or without stone in the common duct, it is frequently completely relieved by four inhalations of amyl nitrite from a 0.3 c.c. pearl. Although the amyl nitrite effect lasts only two minutes, the relaxing effect on the sphincter of Oddi, decompressing the biliary tract and relieving the pain, is often sufficient to break the cycle so that pain frequently does not return for some time. However, nitroglycerin tablets should be prescribed to be taken every 30 minutes if necessary in the event that pain returns. If the pain is not relieved by amyl nitrite, and if after examination the physician is convinced that he is dealing with biliary colic and not an acute cholecystitis or some other surgical abdominal condition, then one of the opiate derivatives may be administered. This should be some drug other than morphine and it should be administered intravenously. Morphine sulfate, when given subcutaneously, must be given in a very large dose in order to relieve the pain. While it acts on the higher centers of the brain to relieve pain, the morphine continues to produce sphincter spasm and back pressure within the biliary tract. After the pain-relieving effect is gone, a residue of drug remains in the subcutaneous tissue that may continue the spasm up to eight hours or longer and result in a return of symptoms. We have seen a case in which 1.35 mg. of morphine was given at 9:00 A.M. in order to test the patient's reaction, following which she became so violently ill that it was necessary to hospitalize her that night. She complained of vomiting and epigastric distress. On the other hand, when a less spasmogenic analgesic is given intravenously, the pain-relieving action is instantaneous. After the drug is destroyed in the body, there is no residue to continue the spasm. The patient should be given nitroglycerin to be taken sublingually every three hours to prevent return of spasm. In addition, a barbiturate should be given to induce sleep. Following this treatment, the biliary colic will probably not return and the patient will remain symptom-free for some time.

4. *Convalescence Following Cholecystectomy:*—(a) *Pain-relieving agents.* If a T-tube has been inserted into the common duct and the bile has free drainage, then one may administer morphine or one of its derivatives for the relief of pain without producing any harm from duodenal spasm. The spasm of the duodenum will not increase the intrabiliary pressure since there is a free flow of bile through the T-tube. On the other hand, the use of morphine may be accompanied by intense nausea. For that reason it is much wiser routinely to use one of the less

spasmogenic derivatives. The choice of drug will depend on the individual patient. In cases in which there is no tube in the bile duct, nitroglycerin 0.43 mg. should be added to each hypodermic dose of pain-relieving narcotic in order to counteract the spasmogenic activity. While the atropine derivatives may be spasmolytic in the case of other types of smooth muscle, we have not found them to be so in the case of the second part of the duodenum and the sphincter of Oddi. The barbiturates should be given in moderate doses in order to cut down on the amount of opiates needed. If the patient is extremely nauseated and vomits a great deal, it may be necessary to discontinue the use of opiate derivatives and depend solely on barbiturates, either intramuscularly or orally, for relief of pain.

(b) *Bile salts* have been reported to be beneficial in the later part of the convalescent period in order to cut down the incidence of postcholecystectomy syndrome. We have, however, had no experience in their administration under these conditions and are not in a position to make any comment on the subject.

5. *Postcholecystectomy Syndrome:*—This may be due to various conditions such as: (1) a missed common duct stone; (2) unresolved pancreatitis; (3) cholangitis; (4) residual stones in a long cystic duct; and (5) a neuroma in the cystic duct. Regardless of the cause, the spasm of the duodenum is a very important factor in continuing the back pressure within the common duct and promoting pain. We have found morphine 11.0 mg. given subcutaneously useful as a diagnostic agent. If this is given to a patient suffering intermittent attacks of postcholecystectomy biliary pain, it will frequently bring on an attack, thus establishing the diagnosis. The attack, however, may be extremely severe and one should be prepared, if the medication is given in the office or clinic, to have some relative on hand to escort the patient to her home.

a. *Antispasmodics:*—Nitroglycerin[25,26], given continuously over a long period of time as described for treatment of cholecystitis, is very often beneficial. The atropine derivatives are beneficial in cases accompanied by pancreatic edema.

b. *Duodenal Drainage:*—If the above treatment fails, then one should institute repeated duodenal drainage, using magnesium sulfate in the following manner: after the duodenal tube has been passd into the duodenum, it is irrigated repeatedly with warm tap water and 60 c.c. of a saturated solution of magnesium sulfate is injected into the duodenum and left there for 30 minutes. The magnesium sulfate is then washed out and the patient is given repeated inhalations of amyl nitrite while the duodenum is being irrigated with warm water. We have obtained considerable benefit with this regimen in intractable cases and have noted considerable amount of pus in the first few drainages, following which the pus usually disappears.

c. *Bile Acids:*—The use of bile acids would probably be beneficial along with this regimen. Here again, we have had a limited experience in their use.

d. *Reoperation:*—If medical regimen fails, then one should consider reoperating upon the patient, diligently examining for a missed large cystic duct, stone or neuroma. The common duct should be opened and explored for stone. If none is found, a T-tube should be left in for prolonged biliary drainage. In a previous

communication, we have laid down the criteria for the duration of T-tube drainage[27]. In one of our cases of postcholecystectomy syndrome so treated, we left the tube in for nine months. She has now been entirely free of pain for a three-year period, whereas, prior to that time she had been ailing for about ten years.

6. *Complications and Sequelae of Gallbladder Disease,* such as pancreatic edema and gastritis, will not be gone into at this time except to say that the pancreatitis is more frequently associated with gallbladder disease than is generally realized. Often the pancreatic edema produces symptoms leading to an erroneous diagnosis of duodenal ulcer. We have seen cases so treated for as long as 25 years without any relief who were completely relieved when the gallbladder was removed and common bile duct drained. During acute exacerbations of pancreatic edema, the condition is generally controlled by a bland diet, the judicious use of atropine derivatives such as tincture of belladonna, 0.6 c.c. three times a day and phenobarbital, 32.0 mg. three times daily.

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DIAPHRAGMATIC HERNIA*

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The protrusion of any organ from the cavity in which it ordinarily lies, or through its tissue confines, is generally spoken of as a hernia. These herniae may carry with them the linings of the original cavity as a hernial sac or the lining of the original cavity may not be present and the hernia will have no such sac. They may be classified as either congenital or acquired. Trauma plays a great role in the etiology of most acquired herniae. However, it is generally felt that an inherent weakness of the tissues through which the hernia makes its exit is frequently, if not always present. Herniations of the abdominal contents through the diaphragm are no exception to these general observations. Most classifications of diaphragmatic herniae, such as those of Richards[1] and Quenu[2], have been made on the basis of the anatomical location of the defect. I would like to propose a very simple classifica-

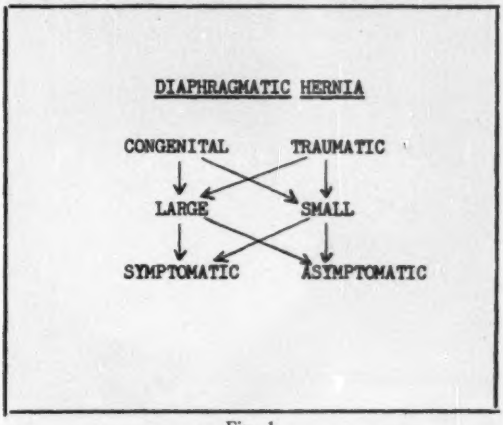

Fig. 1

tion, looking upon these herniae from a clinical and physiological standpoint, and then to discuss a few of the outstanding symptoms with the difficulties encountered in diagnosis.

I feel that there is little clinical importance as to where the herniation is located, whether it be through the natural opening in the diaphragm such as the esophageal hiatus, where most herniae do occur, or through the entrance of the larger nerve trunks or through a tear in the diaphragmatic musculature, except in the pattern of pain that may be produced dependent upon the specific organ which herniates through the diaphragm, or in the pattern of pain produced by displacement of thoracic organs. However, where surgical correction of the hernia is contemplated, there is a great deal of importance in differentiating between large diaphragmatic

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herniae and eventration of the diaphragm[3], since in the latter condition there is no available muscle with which to effect an adequate closure. As can be seen from Fig. 1, the two large classifications of hernia are congenital and traumatic, either of which may be large or small, and either of these may be symptomatic or asymptomatic. It is the symptomatic hernia which is usually the most important, since small asymptomatic herniae rarely cause any difficulty; however, a hernia may be asymptomatic and found by accident, but if it is very large it offers potential dangers and should probably be repaired if there are no contraindications. As to the type of trauma which produces herniae, it may be sudden, as in crushing abdominal injuries, or it may be gradual, as with the steady increase in intraabdominal pressure produced by pregnancy and climaxed by delivery. As you know, herniae through the diaphragm are most frequently seen in middle-aged to elderly females, who have had children,

Fig. 2

are obese, and are of a hyperstenic build. However, this is not the rule, and diaphragmatic herniae are seen in all ages of patients and in both sexes. It is now felt that a great many more males are affected than was formerly supposed[4].

Practically all herniations through the diaphragm are into the mediastinum or into the left thoracic cavity. Symptoms are primarily produced by displacement of thoracic organs, by constriction of the displaced organ by the margin of the opening, or by the spilling of the contents of a hollow viscus in the case of perforation. Small herniae frequently produce symptoms referable to the abdominal viscera, whereas the larger the hernia, the more likely we are to see symptoms of chest disease produced. The typical symptomatology is exemplified by an obese, multiparous female who presents herself complaining of substernal or epigastric distress, either constant or occurring in episodes with radiation to the precordium, the back, and at

times, to the shoulder and arm or to the hypochondrium on either side. She may complain of epigastric fullness and an inability to eat complete meals. Palpitation and shortness of breath may be other disturbing symptoms, particularly if the hernia is a large one. Anything that tends to increase intraabdominal pressure, such as exercise, eating, change in posture, such as stooping or straining at stool, is likely to aggravate the symptoms. Frequently, distress is only present upon lying down and in some patients, only upon lying on the back. Although this is the usual and typical picture presented, there are many variations to the pattern. Dysphagia may be a distressing complaint, as in the patient, shown in Fig. 2, who was a 65-year-old white male. He complained of the onset of his illness six months prior to being seen. He stated that he had had no pain whatsoever and that his only symptom was a progressive difficulty in swallowing, so that at the time seen he was able to swallow only liquids. However, on further questioning, it was found that in eating his liquid meal he felt a low substernal fullness to the point of not being able to swallow any

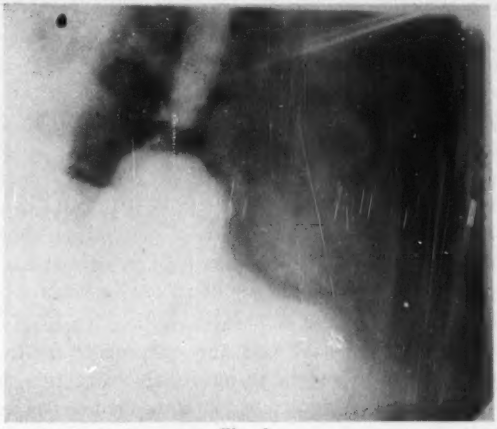

Fig. 3

more. Then, if he forced himself to take more liquids, he frequently would suddenly have complete relief from his symptoms and would be able to eat a solid meal without any difficulty whatsoever. He presented a large diaphragmatic hernia, which probably filled, the filling and stretching of the thoracic portion of the stomach preventing a reduction of the hernia; but when it was forcibly reduced by placing more liquid into it, the symptoms entirely subsided. It is interesting to note, that this patient had no pain whatsoever. Also, the frequency of localization of discomfort in the left hypochondrium should be commented upon. It is usually the type of discomfort and fullness in this area which is so commonly complained of by patients with the irritable colon syndrome. The film in Fig. 3 was made on a white female, aged 44, who had complained of left upper quadrant dull, aching pain particularly at night and when constipated.

The frequency with which diaphragmatic herniae mimic classical pictures of other organic diseases and the frequency with which asymptomatic herniae are

found in the presence of other organic diseases makes one extremely cautious in attributing symptoms to this condition. We frequently see herniae which are entirely asymptomatic as the one in Fig. 4, which was discovered in a 65-year-old woman with a duodenal ulcer. The hernia itself produced no symptoms. One can readily see the extreme importance in differentiating between the symptoms produced by diaphragmatic herniae and those produced by coronary artery disease. Fig. 5 shows a hernia in a male, aged 38, who complained of episodes of constricting lower substernal pain without radiation precipitated by exercise following meals. His entire physical examination was normal. His electrocardiogram was normal. Neither exercise nor adrenalin produced pain or electrocardiographic changes. The hernia was found, and fortunately, when forcibly filled, reproduced the patient's distress. One may see a patient with symptoms suggestive of chronic cholecystitis who has a normal Graham-Cole test and normal biliary drainage with normal upper gastrointestinal x-ray with the exception of a diaphragmatic hernia, and the forceful filling of the hernia may, but does not always, reproduce symptoms. The same may be found in cases presenting typical peptic ulcer stories, and typical symptoms of cardiospasm and malignancy of the stomach or esophagus.

Rupture of a viscus into a thoracic cavity or the strangulation of a diaphragmatic hernia, of course, presents rather striking features of an acute thoracic catastrophe. These may simulate pulmonary embolism, spontaneous pneumothorax or myocardial infarction. They are attended by thoracic pain with radiation to the upper abdomen and the shoulder or arm, marked palpitation, shortness of breath, drop in blood pressure and a cold, clammy skin with or without nausea or vomiting. They are acute surgical emergencies just as the strangulation of a hernia elsewhere.

In the diagnosis of symptomatic diaphragmatic hernia a careful clinical history cannot be overemphasized. As I have said, the symptoms vary from those caused by pressure upon the thoracic viscera to intestinal obstruction, hemorrhage, abdominal pain and dysphagia. A recurrent, obscure anemia has been pointed out as being of frequent occurrence[5]. Frequently, the history is not at all typical, and possibly only one or two points suggest the presence of a hernia. Although the older age groups from 50 to 80 are more frequently found to have herniae, this disorder is fairly frequently found in younger individuals, and should not be overlooked in differential diagnosis. Strangulation, although it does not frequently occur, is seen even though it is felt to be impossible by some workers due to the thick walled, strong musculature of the stomach[6]. The difficulty encountered in the frequency with which this condition mimics other organic abdominal and thoracic diseases is at times distressing. The frequency with which patients who suffer with this condition are labeled as suffering from functional nervous disorders is a point to be contemplated. Suffice it to say that, as with many if not all medical conditions, the more aware we are of the existence of this condition the more it will be diagnosed. Although the clinical diagnosis of diaphragmatic hernia is often times difficult, if not impossible, the presumptive clinical diagnosis is extremely easily confirmed, roentgenographically. No x-ray study of the upper gastrointestinal tract should be

considered complete without an examination in the Trendelenburg position with increased intraabdominal pressure[3]. The esophagoscope plays an extremely important part in detecting early malignant changes in the lower esophagus adjacent to the hernia.

For treatment purposes these patients may be divided into three groups. First, those presenting no symptoms and who require no treatment. Second, those presenting minimal symptoms without evidence of strangulation or obstruction, and third, those patients presenting marked symptoms. In the second group treatment is primarily one of medical management. The use of antispasmodics and antacids may be helpful where indicated. Weight reduction in the obese individual is sometimes of a great deal of help, and may completely eliminate symptoms. The avoidance of overloading the stomach in the few hours prior to bedtime and the use of a bed with elevated head are also helpful in lessening or eliminating the symptoms.

Fig. 4

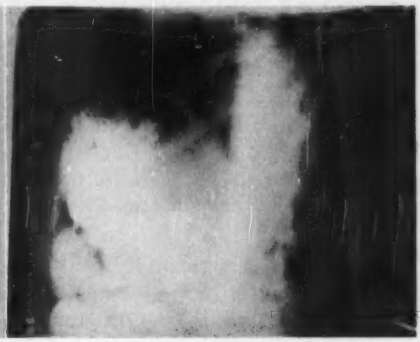

Fig. 5

The third group of patients, presenting severe symptoms, usually will require surgical managment. However, if obstructive symptoms predominate, this obstruction should be relieved as much as possible, medically, prior to the surgical procedure which is chosen. The use of phrenic section with a paralysis of the left leaf of the diaphragm has been very helpful, and is probably the procedure of choice in the older patients who are considered a poor surgical risk for the more strenuous transthoracic repair of the hernia. However, in younger patients and in the older ones whose years are not numbered by coexisting disease, it is probably safest and best to surgically repair the diaphragmatic defect. This may be done from above or below, but the transthoracic approach is considered preferable by most operators.

In conclusion, it may be said that:

1. The diagnosis of diaphragmatic hernia is not a difficult one if the possibility is kept in mind, and if all upper gastrointestinal x-ray studies include the examination of the patient for such a lesion.

2. Although the diagnosis is not difficult, the determination as to whether the symptoms produced are attributable to the diaphragmatic hernia or to some other

condition is often an extremely difficult decision to make, often entailing several months of observation and attendance on the patient through numerous episodes.

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INFECTIVE HEPATITIS*

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Infective Hepatitis

Clinical Signs and Symptoms:—The clinical symptoms of the infective (epidemic) forms of hepatitis are characterized by two stages, the first being the prodromal stage of general septic symptoms, which leads to the second stage characterized, by the appearance of jaundice, which frequently dramatically terminates the generalized septic symptoms. In the second stage the local symptoms of acute hepatitis, and their direct sequelae dominate the clinical picture.

In the benign form, with the establishment of jaundice, the general condition of the patient improves rapidly, the general symptoms subside and there is a gradual and progressive diminution of the jaundice until it clears up entirely within two or three weeks.

In contradistinction to this well marked biphasic course in the *epidemic forms* of hepatitis the clinical course in the *sporadic forms of the gastrointestinal type* might not show any signs of a general infection at all. It appears right from the start as an acute gastrointestinal disorder in the course of which jaundice appears after three to six days.

Prodromal Symptoms in Epidemic Hepatitis:—The onset is usually sudden with signs of a general infection. The initial symptoms are of diagnostic aid only in association with other initial signs of hepatitis, such as edematous enlargement of the liver, or in an epidemic of hepatitis, when suspicion has already been aroused. Sore throat, coryza and other signs of upper respiratory tract infection suggest a droplet or contact infection. Fever is not a regular or characteristic symptom. In some epidemics an initial elevation of temperature between 100° and 102° Fahrenheit has been observed in 80 per cent of the cases (Barker et al[16]); in other epidemics only 50 per cent of the cases were febrile (Hoagland and Shank[17]). Chills are an exception. The uvula is edematous and slightly swollen, and the glands of the neck may be painful. Anorexia, nausea, occasional vomiting, constipation and frontal and retroorbital headache complete the picture of a general infection. In addition to these more characteristic symptoms may be added those of an acute polyarthritis with effusion in various joints coinciding with skin eruptions of a partly allergic character.

Polyarthritis was described as a prodromal sign of acute hepatitis as far back as 1859, by Graves[18]. Recently attention has been drawn to these symptoms by many observers.

Skin eruptions have a definitely allergic character, the most common being urticaria. Otherwise, all varieties of erythemata, petechiae, maculopapular erup-

*This is the third in a series on Hepatitis.

tions, purpura and erythema nodosum have been mentioned. An acneform rash was reported by Flood et al[19]. Since the face is flushed, the icterus presents a characteristic orange color.

Pulse:—There is a tendency to bradycardia. This becomes much more pronounced at the outbreak of jaundice due to the well-known effect of the presence of bile salts in the serum. Tachycardia, with a pulse rate above 110, must be considered as a serious sign, and if persistent and progressive, may be a warning signal that the hepatitis is changing into yellow atrophy.

Blood Changes

Red Cells:—The number of red blood cells is frequently increased at the onset of hepatitis, a fact first noted by Eppinger[20], and since confirmed by many other observers. This phenomenon, most likely, is caused by an effusion of fluids through the capillary walls into the pericapillary spaces, leading to a hemoconcentration. This concentration often parallels a liver edema. The initial relative polycythemia may, in cases of delayed recovery, be followed by anemia with anisocytosis and a tendency to hyperchromia. It is probable that some deficiency of the antianemic factor due to the hepatitis is responsible.

White Cells:—The number of leucocytes increases in the prodromal, preicteric stage, in conformity with the signs of a general infection. An initial leucopenia is observed only exceptionally. With the outbreak of jaundice, the number of white cells drops, and a leucopenia usually sets in, counts of 2,000 and 1,500 having been reported. The differential count shows no fundamental change except a slight relative increase of lymphocytes and monocytes.

Sedimentation Rate:—The sedimentation rate is usually slightly increased and remains so for quite a time after clinical recovery. In the experience of one of the authors (Pribram[21]) a distinct increase in the sedimentation rate up to 40 and 60 is a sign of the development of a complicating cholangitis.

Initial Abdominal Signs

Anorexia is an outstanding symptom, and occurs in 70 to 90 per cent of cases in all series, and as a rule, persists throughout the entire course of the disease. Patients are repelled even by the sight or smell of food, a phenomenon which, in a conditioned reflex, may cause spasm and gastric irritation.

Pain and tenderness in the right upper quadrant of the abdomen and epigastrium are often caused by the initial edematous enlargement of the liver. In some cases pain is severe, and may then, in the not uncommon presence of abdominal distention, lead to an erroneous diagnosis of acute cholecystitis, appendicitis, ruptured peptic ulcer or intestinal obstruction. Severe abdominal pain in the later course of the disease is often due to intramesenteric hemorrhages.

Onset of Jaundice:—With the onset of jaundice, the entire clinical picture of a general infection may, in many instances, change dramatically. This fact, observed by most authors, gains in pathological significance from the simultaneous cessation of infectivity and disappearance of the infective viruses or of their pathogenic properties. Even central nervous symptoms, such as drowsiness, restlessness,

and signs suggesting encephalitis or meningitis, may disappear completely with the onset of jaundice in cases with a favorable prognosis. The general condition of the patient may improve and he may even regain his appetite.

Special attention has been directed to the fact that jaundice will relieve the pain and symptoms of arthritis. D. L. Wyatt, as well as Hench[22], reported a group of cases in which an attempt was made to reproduce this effect by the intravenous injection of bile salts and bilirubin. The results, however, which were obtained were not comparable to those observed in genuine hepatitis. Nor did artificially transmitted jaundice have the same effect. It would seem that the bile has properties which are detrimental to the virulence of these viruses, so that by inflicting damage to the liver parenchyma and releasing an effusion of bile into the blood stream, the viruses are, so to speak, digging their own grave. The intensity of the jaundice may be considerable from the beginning, the index often reaching a much higher level than in obstruction due to gallstones. Serum bilirubin figures as high as 40 mg. per 100 c.c. of blood may be observed. Both forms of bilirubin, i.e., reticulo- and hepatorubin, are present in the serum, with the latter predominating at the height of the disease. In contradistinction to the above-mentioned favorable turn in the general septic condition observed in many instances at the onset of jaundice, the gastrointestinal symptoms may become considerably worse at this time.

Anicteric Forms:—Jaundice, although doubtless the chief symptom, in most cases of epidemic jaundice, is absent in certain cases and in a few epidemics is present only in a minority of cases. Williams[23] reported an incidence of 1.6 per cent of nonicteric cases in a New York epidemic including 700 patients. Hartfall[24] reported 7 per cent of subicteric cases in a Malta epidemic of 450 cases. Gowen[25], basing his diagnosis of epidemic hepatitis on the elevated serum icterus index, claims that cases without jaundice may be 8 times as frequent as those with jaundice. Pollack[26] concludes from his observations that the incidence of anicteric hepatitis in epidemic hepatitis varies from 10 to 20 per cent.

The clinical symptoms of the prodromal stage and those of the later course in the anicteric cases may be identical with those seen in cases of fully developed jaundice in the same epidemic. Likewise, positive liver tests indicate a similar liver damage. The serum icterus index may be normal in some instances and only slightly elevated in others.

The existence of anicteric forms of hepatitis in spite of extensive liver damage, cannot be easily explained by the former concepts of the etiology of hepatojaundice. Bearing in mind, however, that the excretory function of the liver cell is only a partial function, which may or may not be impaired in hepatitis, and that the excretory block is probably of neurotoxic origin, this variation in symptomatology is less difficult to understand. In most instances the anicteric cases of hepatitis are mild and go on to full recovery within 2 weeks. They may be considered as abortive forms of infective hepatitis. In some epidemics, however, the cases without jaundice may run a fulminating course with a high mortality rate and death ensuing within 10 days (Lucke[27], Pavel[28], Taylor[29], Wood[30]). The

clinical symptoms in such cases often point from the very beginning to lesions of the brain-stem, caused, no doubt, by some neurotrope virus strains.

Liver:—A moderate enlargement of the liver is observed in practically all cases. The size varies greatly, however. We have seen cases in which the liver extended down to the umbilicus, even before the onset of jaundice. In these instances it was an acute edematous swelling like that observed in allergic liver conditions. When jaundice appeared, the liver diminished somewhat in size. Pain in the epigastrium and right hypochondrium is a common and frequently an early prodromal sign. Severe abdominal pain simulating that of acute appendicitis sometimes leads to diagnostic errors (Turner et al[31]). Such severe pain may be explained by the finding of mesenteric hemorrhages which are frequently observed, e.g., in Weil's disease.

Spleen:—Enlargement of the spleen is inconstant and is observed more frequently in cases with a protracted course. Secondary enlargement of the spleen indicates damage to the vascular framework and development of cirrhosis.

Duodenal drainage:—A certain amount of bright yellow bile may be present in the duodenum. This, however, varies. On some days no bile at all may be found. The most striking observation is that *B-bile cannot be obtained in a single instance.* Paralysis of the gallbladder and excretory block of the liver cells which can no longer discharge the stored pigment, may account for this interesting fact.

Kidneys:—Albuminuria is observed in a certain percentage of cases, in 18.5 per cent, according to Hayman. Greater quantities of albumin and signs of anuria and uremia suggest Weil's disease. Turner found the concentration power of the kidneys defective in 11 out of 15 cases.

Stools:—In the majority of average cases the stools are not completely acholic. They are light colored, but in spite of their clay-like appearance may contain stercobilin up to 30 mg. or more in a 24-hour specimen (Rappaport[32]). The frequent finding of occult blood in the stools is mentioned by many authors (Lucke[33], Pollack et al[34]), who attributed it to a hemorrhagic tendency or colitis. In the series of one of the authors (Pribram) of this article the discovery of painless duodenal ulcers offered an unexpected explanation of this fact.

Recently Lucke and Mallory[35] reported the outbreak of a "fulminant form" of epidemic hepatitis. Twenty-seven out of 196 cases with a fatal issue within 10 days were presumed to be homologous serum hepatitis following trauma, plus transfusion of blood or blood derivatives. The total mortality rate was 39 per cent. The serum hepatitis tended to run a considerably more rapid course than the "naturally" occurring disease. Otherwise there were no clinical or pathological differences.

The authors were also able to distinguish two types of the disease: an infectious type with high fever, dizziness, malaise and general aching; and a gastrointestinal type with anorexia, nausea and epigastric discomfort. It was found worthy of mention that in contrast to the deep jaundice commonly observed in the subacute and milder forms, the degree of jaundice in the fulminant cases was only slight, and there were several nonicteric cases. The liver lesion was characterized by extreme

destruction and uniform involvement. Inflammatory infiltration was most conspicuous at the lobular peripheries and less pronounced within the lobules. Regeneration was only minimal and confined to reconstruction of the bile ducts. The changes in the brain were those of a mild encephalopathy. Ascites was present in 25 per cent of the cases.

The authors came to the conclusion, significant in relation to the conceptions of the importance of sensitizers as developed by Pribram[36], that "interrelated factors, such as fatigue, trauma, and nutritional disturbance of the host, rather than the strain or the amount of the infectious agent, played a dominant role."

Liver Function Tests

During the last war liver function tests were carried out on a large scale in cases of epidemic and serum hepatitis. The results were much more encouraging than had been expected. Most observers were quite satisfied with the results and, indeed, it seems that the much contested practical value of such tests is now established. This is especially true when after full clinical recovery, liver function tests still indicate some residual liver damage and hepatic insufficiency, suggesting further careful observation and treatment.

In the acute stages most liver tests are positive. In mild cases the excretory function only is blocked. Hanger's cephalin flocculation test and the combined thymol turbidity and flocculation test have the highest sensitivity. They are found positive in many instances for a considerable time after recovery.

The significance of response to attempted correction of the delayed prothrombin clotting time, by the administration of Vitamin K, has been especially emphasized by Lord and Andrus[37], Ford et al[38], and Turner[39] and his associates. A prompt response to injection of Vitamin K indicates a good prognosis, while a delayed improvement or complete failure to respond must be considered as a serious sign of occasionally irreparable liver damage. These authors consider response to Vitamin K therapy the best simple prognostic guide.

"Screening" of the liver function with several tests has been advocated by many authors (C. J. Watson[40], Mateer et al[41]). A plan in testing liver function is certainly of great value.

C. J. Watson recommends four procedures:

1. Icterus index (fasting).
2. Urine-urobilinogen (serial qualitative test).
3. Cephalin-cholesterol flocculation test.
4. Bromsulphalein, 2 mg. per 20 kilo.

The problem encountered in the evaluation of liver tests is the following: The less sensitive liver tests may be negative in spite of liver damage, while other tests, such as the cephalin-flocculation test, are more sensitive than required for practical clinical purposes and, moreover, this latter test is not specific.

G. Mateer developed a combined screening method based on the therapeutic response. His method of examination is as follows:

1. When a screening test with the more sensitive liver function tests is positive, less sensitive tests are used subsequently in an attempt to determine the degree of impairment of the liver.

2. Patients with positive results with the more sensitive liver function tests are routinely subjected to intensive liver therapy.

The time required for these sensitive tests to return to normal is recorded. The length of time required varies from 7 days to 15 months. This therapeutic test to evaluate the positive results of sensitive liver tests permits an early diagnosis and provides an opportunity for early treatment.

The advantages of this procedure have been summarized by Mateer as follows:

1. A refinement of the interpretation of the sensitive tests as to the approximate degree of impairment present.

2. Measurement of the magnitude of the therapeutic problem in each case.

3. Importance of early effective treatment of such patients before an advanced stage of hepatic disease has developed.

Clinical Course of Acute Hepatitis

The disease may develop in different ways, according to the amount of liver damage involvement, and also dependent upon the particular properties of the infecting virus-strain.

I. *The Benign Form:*—The general condition of the patient improves rapidly, jaundice subsides within 2 or 3 weeks, the patient recovers quickly and there is no mortality.

II. *The Vascular Form:*—The vascular framework of the liver suffers early damage and within a few weeks symptoms of a vascular cirrhosis with varicosities and hemorrhagic tendencies may develop. These lesions are not irreversible, however, and may heal completely. The mortality rate in this variety ranged from 5 to 10 per cent.

III. *The Neurocerebral Form:*—In this form there are early symptoms of damage to the central nervous system. The disease may run the course of an acute atrophy of the liver with a mortality rate as high as 40 to 60 per cent.

IV. *The Gastrointestinal Form:*—From the very onset the course in this variety is monophasic and more like that of a gastrointestinal intoxication. Gastrointestinal as well as pancreatic syndromes may prevail during the entire course of the disease.

Both epidemic and serum hepatitis may develop according to the sequence described under I, II or III, whereas the pure gastrointestinal form is hardly ever observed in serum hepatitis, and is not frequent in real epidemics. This form is more commonly observed in the sporadic cases.

V. *The Vascular Form:*—In this variety the leading symptoms include the early development of ascites, varicose veins, and a hemorrhagic tendency.

Ascites

Turner[42] observed 13 patients with ascites in his epidemic, and believes that capillary injury is to blame for this symptom. Ascites was observed as early as the

seventh day after the onset of the disease; in another case it appeared on the seventeenth day; and in one instance on the seventy-fifth day of the illness. Ascites may subside spontaneously with improvement in the general condition of the patient. In some of the patients with ascites, the history revealed some previous liver damage, such as malaria.

One of the most remarkable observations is the fact that damage and destruction in the portal vein system may be followed within a rather short period by the appearance of enormous amounts of ascites, up to 10 and 20 liters. It is also worthy of mention that in spite of signs of serious portal obstruction leading to ascites, on one hand, and inflammation of varicose veins, on the other hand, the damage to the vascular framework may subside completely.

Serious hemorrhages into the intestinal tract and abdominal cavity may cause early death (Turner). Severe attacks of pain in the lower abdomen, sometimes suggestive of acute appendicitis, were explained at postmortem as being due to hemorrhages into the mesenteries. Gingival bleeding may present a serious complication at the height of the illness. The gums may become inflamed, bleed easily and become hypertrophied. Fatal bleeding from varicose veins in the esophagus was observed only a few weeks after the onset of the disease by Turner.

The tendency to a hemorrhagic diathesis depends on at least three different factors:

1. The inability of the diseased liver to maintain the normal prothrombin level.
2. The toxic damage to the capillaries, probably caused directly by the infective agents or toxins.
3. The damage done to the vascular framework of the liver, especially the portal branches, leading to venous congestion, portal hypertension, ascites and hemorrhages from varicose veins. This process also is not irreversible and may well subside with improvement of the hepatic condition within a surprisingly short period.

Angiomata and Telangiectasia (Spider-nevi)

The incidence of spider-nevi during the course of chronic diseases of the liver and especially in those of a cirrhotic type, has long been recognized. It has, however, been noted that in quite a few cases of acute infective hepatitis spider-nevi may develop in the early stages of the disease (Noel-Fiessinger[43], Williams and Snell[44], Lichtman[45], Damodoran and Hartfall[46], C. J. Watson[47], and one of the present authors). C. J. Watson has emphasized the fact that multiple spider-nevi are observed exclusively in diseases of the liver. Of practical significance is the fact that these angiomata may disappear as the liver condition improves, thus this is a sign of apparent prognostic value. The question arises whether these telangiectasia are just the signs or sequelae of a stasis in the portal circulation, ranking with acute ascites and the development of varicose veins in the esophagus and intestines, or whether they represent a direct damage to the capillaries.

The Neuro-Cerebral Form:—Nervous symptoms may be pronounced from the very outset. Their presence is a serious sign and suggests a poor prognosis. This is especially true if the initial nervous symptoms do not subside with the outbreak of

jaundice, but persist or become worse. It is a well-known fact that when the disease begins with striking symptoms of restlessness, crying, etc., it very frequently will run the course of a fatal yellow atrophy. In Turner's epidemic (serum hepatitis) all except two of the patients who showed severe central nervous symptoms died, all those who died presented symptoms before death. A change in personality is one of the early symptoms. Soldiers who were previously most correct in their behavior, became carelss and rude, restless and resentful. Impairment of speech is frequently observed, either in the form of loquacity or incoherency. Hallucinations and restlessness sometimes change quickly into stupor and coma. Crying is frequently observed. The mental state occasionally changes during the day, becoming worse at night. Patients become angry, noisy and intolerant of their surroundings. Amongst other nervous symptoms, tremor of the hands and fingers and ankle clonus may appear and disappear. A positive Babinski reflex has not been observed. In most patients with nervous symptoms, tremor has been the most striking sign, and the knees shake while the patient is standing (Turner). The reason for this is not quite clear. The association of jaundice and brain symptoms, such as delirium, convulsions and fatal coma, has been observed since antiquity, and such symptoms were attributed to the absorption of bile into the blood. "*Bilis ut plurimum insaniae causa*" (Hippocrates) and "*bilis ad caput recurrent delirii causa*" (Galenus). However, experimental injection of bile into the veins of dogs, carried out by Frerichs, and repeated by many other observers, did not in any instance produce cerebral symptoms. Protracted experimental cholemia, conforming with clinical observations, has also proved beyond doubt that the presence of bile in the blood alone cannot be blamed for the cerebral symptoms. Two alternatives remain open for discussion: First, intoxication by products of the broken-down liver tissue which are absorbed into the blood stream, and, second, direct affection of the brain by a neurotropic virus. Experience in epidemic hepatitis and in postvaccination serum hepatitis is quite compatible with the latter conception. In some instances severe symptoms appear even in the very early stages. In these cases there can be no question of any breaking down of liver tissue on any such scale as that occurring in acute yellow atrophy. The potential neurotropic properties of the yellow fever virus, on the other hand, are well known. The polytropic pathogenic properties probably become manifest only shortly after invasion (skin, joints, brain, etc.) before the infecting viruses "specialize" in the liver.

The (Sporadic) Gastrointestinal Form:—There are quite sound reasons for separating this form of icteric hepatitis from the septic epidemic forms described above. The histories of two patients, both intelligent observers, who were under our care in the hospital almost at the same time, may serve as an introduction:

Case 1:—A business man of 42 gave the following history:

"Without any warning symptoms I was suddenly taken ill with slight rigors and shivering; my temperature rose to 102. Believing it was influenza, I took some aspirin. My appetite was all right and I had my usual meals and went to my office. I was sweating profusely and my temperature, which had dropped after taking the aspirin, rose again. I retired early. The next morning I had a sore

throat and slight cough, but on the whole felt better and ate breakfast. At this time my appetite was fairly good. Later my temperature again became elevated and I was perspiring profusely. Aching in my head, back and joints ensued. I was positive I was suffering from influenza and remained in bed. There was no improvement in my condition, I lost my appetite and had a sensation of weight in the stomach. Four days after the onset of the illness, I called a doctor and was treated for influenza. My temperature subsided slowly, but the urine became dark, the stools were pale, and jaundice appeared."

Weil's disease was excluded in this case by absence of renal symptoms of leptospira and by serum tests, and the diagnosis of infective hepatitis was established.

Case 2:—A man of 35 described the onset of the disease as follows:

"I had not been ill for nearly twenty years except for a few insignificant colds. Years ago I had an attack of fever (perhaps it was malaria). I was in perfect health. I attended a dinner last week with some friends. Having had no lunch I consumed large quantities of food. I also had several drinks. I arrived home at 2:00 a.m. and did not sleep well. I awoke in the morning with the taste of the dinner still in my mouth and began to belch. I experienced slight headache, but had no fever and did not feel ill otherwise. I intended to take some epsom salts immediately, but changed my mind as I had to go to the office and was late. I took some coffee at breakfast, but did not eat any lunch. During the day I felt better. Nausea, however, persisted, as also did the fatty taste in my mouth. There was a feeling of undue pressure in the epigastrium. I took a mild laxative. The following day I felt better. On the third day after the dinner I noticed that my urine was dark brown, and my wife told me that I looked yellow. On the following days my stools were acholic and fatty in character. The disease cleared up within six weeks under appropriate treatment."

Whereas there can hardly be any doubt as to the infective character of the epidemic forms of hepatitis, a good deal may and has been said favoring the theory that the gastrointestinal form is a purely toxic hepatitis following some kind of food poisoning.

In the septic forms of epidemic hepatitis there is a definite incubation period lasting about 22-24 days. The initial clinical symptoms of the prodromal stage show all the characteristics of a general septic infection, in which the symptoms may disappear with the outbreak of jaundice. The biphasic course of the disease is well marked.

In the purely gastrointestinal form the initial clinical symptoms start immediately following ingestion of a suspected meal which does not agree with the patient. Obviously this gives the impression of food poisoning or acute indigestion rather than an infection. This acute indigestion, as seen in the case just described, may, within a few days, give way to the clinical picture of an acute icteric hepatitis. In its onset and clinical course this type conforms to the description of a gastroduodenal catarrh, complicated by jaundice, or the so-called catarrhal jaundice of the older authors. In the histories of these patients no indication was ever

given of an infection through contact with another diseased person. If an infection was to be considered, the germs could have been transmitted only through the suspected meal. In fact, such an infection, via the alimentary tract with germs of the paratyphoid or botulinus group, has been assumed by some French writers. The following case may throw some light on this problem and may furnish a clue to its solution:

A man who had sustained a fracture of the leg had been in bed under traction treatment for seven weeks. He had had no contact with any patient suffering from hepatitis and had never received any transfusion of plasma or blood. After removal of the traction the leg was placed in a plaster cast. The patient then requested permission to spend a day with his son 14 years of age, who was to celebrate his birthday, although he was sick in bed with fever. It transpired that the boy was suffering from infective hepatitis. There was a current mild epidemic of this disease, in which the regular incubation period varied from 22 to 23 days. The father remained at home with his son for two days. During this time he indulged heavily in food and drink. On the third day he returned to the hospital. At this time he presented all the signs of acute indigestion and had not completely recovered from his alcoholic excess. Five days later, i.e., eight days after exposure to the infected child, the father developed icterus and hepatitis.

This case is very suggestive. The overindulgence in food and alcohol, followed by acute indigestion, had obviously caused some liver damage. The viruses transmitted from the infected child thus found a fertilized liver which was well suited for the rapid development of acute hepatitis in the short incubation period of eight days, as compared with the usual 22 days. Supposing a healthy virus-carrier be taken ill with an acute attack of indigestion and toxic liver damage, such a person with a sensitized liver might develop acute hepatitis which might not develop in the absence of liver damage. The first symptoms observed in the patient during an attack of acute indigestion are not those of the viral infection: they are the symptoms of sensitization which in one phase might pass into those of an acute viral hepatitis. A comparison with the onset of a common cold, also a viral infection, has been cited. The early symptoms observed almost immediately following exposure to cold weather, the explosive edema of the mucous membranes, etc., are the symptoms of damage to the capillary walls due to capillary contraction and anoxemia with consequent effusion of fluid. These initial symptoms of sensitization are followed after a due incubation period of one or two days by those of the spreading viral infection.

Clinical Syndromes of the Intestinal Tract

In all forms of acute infective hepatitis, gastrointestinal syndromes of varying intensity may develop. These symptoms are very pronounced in some epidemics, including cases of acute yellow atrophy. In serum-hepatitis they are usually less pronounced. In some cases the gastrointestinal syndromes, including acute duodenitis, pancreatitis and also a secondary cholangitis, may dominate the clinical picture.

Duodenitis:—The importance of duodenitis in catarrhal jaundice has long been recognized. Broussais[48] mentions it as far back as 1825 with the conception of an ascending spread into the biliary system. Stokes (1839)[49], in his lectures, stressed the importance of inflammation of the upper digestive tube in the development of jaundice. He emphasized, however, that the jaundice is *independent of any mechanical obstruction of the gallbladder* or biliary ducts and believed that in gastric or duodenal irritation the liver is involved *sympathetically* with resultant inhibition of biliary secretion. This conception, more than one hundred years old, comes very close to our own conclusions drawn from a review of the literature and our own observations. We have somewhat lost sight of the important clinical significance of duodenitis in the course of infective hepatitis, and very little is to be found on this subject in the text books.

Virchow was impressed by the existence of duodenal catarrh, but his theory of mechanical obstruction of the papilla by catarrhal débris was severely criticized, resulting in subsequent underestimation and neglect of this pathological feature. However, leaving aside etiologic speculations, this pathological feature of duodenitis, restricted mainly to the second part of the duodenum, deserves our full attention. The anatomical changes include varying degrees of congestion and edematous swelling of the mucous membranes. Mucus and a whitish fluid containing varying amounts of white cells and epithelial débris are present.

On attempting to introduce a duodenal tube great difficulty is frequently encountered in passing it through the pylorus. When bile is obtained at all it is of a light yellowish color and rarely normal yellowish-brown. In some cases only a whitish mucoid fluid, obviously derived from the bile duct system, is seen. *B-bile cannot be obtained in a single case.* This observation has been recorded by all investigators and is characteristic and important. Obviously, it indicates that the *gallbladder does not contract and empty in spite of a patent sphincter of Oddi, and, moreover, that the liver cells are likewise unable to empty their stores.* Routine roentgenological examination of the duodenum, although rarely carried out, is enlightening in this respect.

Spastic contraction can be seen in the beginning. In the later stages, however, there is a pronounced dilatation of the second part of the duodenum, slowing down in the passage of the barium meal, and complete stasis in this part of the organ. One sometimes receives the impression of a duodenal obstruction. On pressure, however, the contents can easily be propelled down into the jejunum. One may, therefore, assume a toxic paralytic state of the duodenum. The existence of such a duodenal stasis was demonstrated in a remarkable case reported by H. Barber and S. R. Osborne as clearly as in a deliberately performed experiment.

These authors had the rare opportunity of studying the morbid anatomy of acute icteric hepatitis in a man who died by accident in the first stage of the disease on the seventh day after development of jaundice. The duodenum was of normal size and contained much tenacious white mucus and no bile but a number of droplets of bright metallic mercury. The patient drank the mercury droplets with a glass of water, over which the nurse had broken a thermometer *four* days

previously. No mercury could be found beyond the *second part* of the duodenum, thus proving that the stasis had lasted for at least four days and was limited to this part only.

What is the cause of duodenal paralysis, and what connection has it with the development of icterus and hepatitis?

Virchow's theory that catarrhal jaundice is actually an obstructive jaundice, caused by occlusion of the sphincter of Oddi, has been revived by Pavel and his associates. They attach great importance to spasm of the sphincter of Oddi. Pavel and Jovin observed in roentgenological examinations that spastic duodenitis occurred in the preicteric stage of the disease. In recurrent attacks of jaundice due to hepatitis these authors carried out parallel liver function tests and roentgen ray examinations of the duodenum. They found that the exacerbation of jaundice coincided with the exacerbation of duodenitis. They concluded that spastic contraction of the sphincter of Oddi in the course of duodenitis, and not hepatitis, is the actual cause of the recurrence of jaundice. The existence of such a spasm in the course of catarrhal jaundice, putting aside for the moment the question of whether this spasm is actually the cause of the jaundice, was clearly demonstrated in a case of severe jaundice operated upon by one of the authors of this article.

Common duct drainage had been established and yellow bile drained freely from the tube on the day following operation. When the rubber tube was reopened after being closed for a few hours, epigastric pressure was immediately relieved and a large quantity of bile drained through the tube. There is no doubt about the *occasional* existence of a spasm of the sphincter of Oddi. It is more probable, however, that this spasm is merely a complicating factor and not the actual *cause* of catarrhal jaundice. The whole character of this disease in all its manifestations is fundamentally different than an obstructive jaundice. One gets a very positive impression of this at operation. There are no signs of stasis in the common duct, no dilatation of the wall, and when bile is at all present, it is light yellow or whitish, and very rarely dark green as is the case in bile stasis.

The gallbladder is often distended, but slight pressure suffices to empty it, thus proving that stasis of the gallbladder is due to a lack of contractility, the result of an *atonic paralytic* state. The bile ducts are occasionally filled with a whitish, turbid fluid.

The clinical triad of *paralysis of the second part of the duodenum, paralysis of the entire cholekinetic tube system, including the gallbladder*, and *intracellular excretory block*, suggests a *toxic neuroinhibition* located in the common centers of the hepatic branches of the splanchnic nerve.

Painless (Trophic?) Duodenal Ulcers:—In three instances of a series of 12 cases operated upon for hepatojaundice one of the writers of this article has seen duodenal ulcers associated with catarrhal jaundice, and they were all characterized by the fact that they were completely painless. In one case ulcer was diagnosed incidental to one of the serial roentgenological examinations, and in another case, the ulcer ruptured *without causing any pain or other* clinical symptoms. The history of this case is recorded elsewhere (Pribram)[50].

Multiple erosions and ulcerations have been observed in the duodenum in many instances of icteric hepatitis, and at postmortem of patients who died of yellow atrophy. If we accept the working hypothesis of toxic damage to the nervous centers, which covers the regulation of cellular excretion of bile, its expulsion through the whole biliary duct system and the kinetic duodenal cooperation, we are better able to understand the entire clinical picture.

Complicating syndromes in the gastrointestinal tract, including severe duodenitis, pancreatitis and cholangitis are apparently less frequent in the epidemic forms and in serum-hepatitis. Recently Van Rooyen and Gordon[51] have again examined the duodenum thoroughly with the duodenal tube in cases of epidemic hepatitis and could find no evidence whatsoever of duodenal catarrh.

Pancreatitis as a Symptom in Catarrhal Jaundice:—Observations of pancreatitis in cases of catarrhal jaundice have been rare up to the present time. Surgeons have, however, reported that in operations for prolonged jaundice the head of the pancreas has been found swollen and indurated. The idea that pancreatitis, that is to say, the swelling of the head of the pancreas, might cause obstruction of the lowest part of the common duct, was put forward by Mayo-Robson[52] in 1900. He writes: "I believe the usual course of so-called catarrhal jaundice is the extension of the inflammation from the duodenum to the pancreatic duct, with a consequent pancreatitis, and as the common bile duct passes through the pancreas in 62 per cent of cases, it necessarily follows that swelling of the head of the pancreas may, by pressure on the bile duct, lead to obstruction of the bile flow and so to jaundice." Carrie[53] has the same conception of the primary role of pancreatitis in the pathology of catarrhal jaundice. He believes that the epigastric pain frequently observed in acute hepatitis is actually due to pancreatitis. Very few biopsy and postmortem findings, but quite a number of clinical observations, have been reported confirming the frequency of simultaneous involvement of the liver and pancreas with similar functional damage. As already pointed out on many occasions, the first sign of liver damage is the fleeting edema which causes considerable enlargement of this organ. The same holds good for the pancreas. The head becomes enlarged, but as the capsule is rather firm and the whole organ cannot expand freely downward into the abdominal cavity, its consistency becomes very hard, especially at the head.

Round cell infiltration takes place more easily and freely, thus increasing the firmness of the head of the pancreas, the lobules of which sometimes feel like stones. The indurated pancreatic tissue surrounding the ampulla might, under certain circumstances, cause complete compression of the opening of the common duct into the duodenum. The resultant stasis in the biliary system adds another complication to the pathological features of hepatitis. Stasis in the pancreas is also observed with resultant increase in the amylase content of the blood, as demonstrated by Pavel[54].

The French school, with Carnot and Loeper[55] et al consider catarrhal jaundice the result of angiohepatitis and angiopancreatitis. Considerable clinical research work has been done in an attempt to prove or reject this conception, by an

examination of pancreatic function in catarrhal jaundice (Cathala, Bolzers[56], Weil[57], Chiray[58], Libbon and Maire[59], Loeper[60], Pavel[61]). These examinations showed that in most cases there is a definite diminution of the activity of the pancreatic lipases. However, the value of these observations is diminished by the following facts: In order to develop their fat-splitting activity, the lipases require the help of activators. Such activators are carried with the bile into the duodenum; they are the bile salts and the much stronger and almost specific activator, cholecysmon, the hormone discovered in the wall of the gallbladder (Pribram[62]). Consequently the diminished activity of lipases in the duodenal juice, free of bile and activators, permits only very limited conclusions as to the role played by a diseased pancreas. Bolgert et al[63] believe from their observations that the drop in lipases is in some cases so considerable that it cannot be explained by the lack of activators alone. Pavel et al[64] found an increase of amylase in the urine in 85.7 per cent of their cases. Other clinical observations, like the appearance of an excess of neutral fat in the feces, also suggests involvement of the pancreas. The endocrine activity in catarrhal jaundice has been investigated by Boller and Uberack, Lupo et al, Pavel, Florian and others. It was found that the *tolerance for insulin* is greatly increased in patients with catarrhal jaundice as compared with normal persons. They reported, in one case, an increase of insulin tolerance up to 120 and 210 units. A curve indicating the insulin tolerance parallels the results of the galactose test. The conclusion, therefore, is that in addition to the inability of the liver to store glycogen, there is an insufficiency of the islets of the pancreas. This would indicate that in some cases the galactose test is not purely a liver function test, but rather a combined test for hepatic and pancreatic function. This concept could well explain the many clinical observations that sugar tolerance tests do not always indicate the same degree of hepatic insufficiency as that indicated by other tests.

Homologous Serum Hepatitis

This variety of hepatitis is characterized by the fact that serum from a healthy donor may convey an infective hepatitis to another healthy person, after a prolonged period of incubation varying from 2 months to 6 months. It has, further, been established clinically that this disease is not infective to other persons by contact and is transmitted only by parenteral injections.

The historical background of this disease dates from 1883 when Hirsch[65] reported 191 cases of jaundice in a series of 1,289 persons vaccinated with humanized lymph in glycerin in which the incubation period varied from several weeks to a couple of months. It was evident that a particular lymph was responsible for this incident because 500 persons vaccinated with a different lymph did not develop jaundice.

Homologous serum hepatitis has been observed following vaccination against yellow fever, mumps, etc.

Many years passed and it was not until 1937 that two children in Oxford, England, died on successive days of acute yellow atrophy of the liver, and within two months there were 3 more cases of fatal yellow atrophy, all 5 of which could be traced to injections from the same source, namely, measles convalescent serum.

The entire group of 109 recipients of this batch of serum were traced and it was found that 41 were taken ill with homologous serum jaundice, of whom 8 died of hepatic necrosis, i.e., a mortality of 12 per cent.

Cases of jaundice following yellow fever vaccination have been observed in different parts of the world—Brazil, Egypt, and West Africa. In Brazil, in 1939, 27 per cent of a group of 304 persons vaccinated with yellow fever vaccine were taken ill with jaundice. In another similar series of over 100,000 cases, 1,027, or one per cent, became icteric. The largest series reported was in the United States Army personnel, 28,585 cases with 62 deaths from homologous serum jaundice.

Oliphant[66], studying an outbreak of homologous serum hepatitis following yellow fever vaccination in the islands of St. Thomas and St. John, found that symptoms of hepatitis developed in 14.7 per cent of 11,358 individuals.

Findlay and MacCallum[67] and their coworkers established the fact that the hepatitis which followed yellow fever immunization was not in any way dependent upon the yellow fever virus, but due to some agent in the human serum used in the preparation of the vaccine. As a result of this discovery the technic of preparing the serum was altered, first, by using only those donors who remained healthy for over a month after the serum had been withdrawn, and, secondly by activating the serum through heating it at 56 degrees Fahrenheit. Following these precautions not a single case of jaundice developed.

Sawyer[68] in a study of the source of the infective agent of homologous serum hepatitis, demonstrated in a convincing manner that the yellow fever virus could be entirely eliminated. The infective agent was in the human immune serum. This infective agent varied greatly in different batches of vaccine. For instance, in one lot homologous serum jaundice occurred in 56.64 per thousand cases, but in another group in the United States Army there was only 0.41 per thousand cases, this figure falling within the normal expectations.

The next pertinent question was whether the infective agent in this disease is present in the feces, as occurs in epidemic hepatitis. J. R. Neefe[69] and others reported that pooled specimens of feces from 6 patients suffering from serum hepatitis in various stages, were administered orally to 19 volunteers, none of whom showed any signs of homologous serum jaundice. This established the fact that the causative agent was not present in the stool. Directly opposite results were obtained in an experiment where the pooled feces of patients with infective hepatitis were used and within 26 days 6 of 12 volunteers developed hepatitis.

It has been established that the infective agent of homologous serum hepatitis is not identical with the presumed virus which causes infective hepatitis, based upon the following facts:

1. The incubation period in homologous serum hepatitis is always over 60 days, and may be 6 months or more, while the usual incubation period in epidemic hepatitis is between 25 and 40 days. It is not possible to postulate that the etiological factors that produce such different periods of incubation can be identical substances.

2. Route of infection: Contaminated water or food and contact infection may produce infective hepatitis, whereas serum hepatitis can be conveyed only by parenteral inoculation. Contact transmission has never been observed.

A contact source of infective hepatitis was established in Egypt when British troops occupied quarters vacated by Germans who had had infective hepatitis. In these instances infection could only have been caused by contact—food, water supply or vectors of some type.

The difference in identity of homologous serum hepatitis and epidemic hepatitis is further established by the fact that there is no cross-immunity. H. B. Haven[70] supported this belief in the lack of cross-immunity by inoculating 3 volunteers who had suffered from homologous serum hepatitis six months before, with infective epidemic hepatitis material obtained in the preicteric stage. All 3 developed infective hepatitis after an incubation period of 25 days.

It has been shown that the infectivity of epidemic hepatitis is confined to the preicteric stage, that the infectivity subsides quickly after the onset of jaundice, and that there is no infectivity following recovery. The infective agent of serum hepatitis on the other hand is present in carriers who show no signs of the disease at all.

The aforementioned observations establish the fact that the infective agents of these two diseases are different in nature. They have, however, these characteristics in common, namely, that they both pass through Seitz filters and withstand heating to 56 degrees Fahrenheit for 30 minutes.

	Infectious Hepatitis	Homologous Serum Hepatitis
Etiology:	An unknown virus which passes through a Seitz filter and survives heating to 56 degrees Fahrenheit for 30 minutes.	Same.
	This organism has been isolated from the secretions of the nose, mouth, throat, duodenal juices, feces and blood.	From blood only.
Incubation Period:	7 to 40 days.	40 to 210 days.
Experimental Transmission:	May be accomplished by various routes, oral, intranasal and parenteral. Parenteral transmisson fails occasionally.	Parenteral only.
Immunity:	No absolute immunity exists.	Reported only in one series of cases (*Oliphant*).

No cross-immunity exists between the two diseases (MacFarlane et al[71], Havens).

On the contrary, the occurrence of one disease renders the person more susceptible to invasion of the other type of hepatitis. The initial attack of hepatitis weakens liver resistance and renders the organ more susceptible to an attack by a second infection.

W. H. Bradley[72] and others described an outbreak of icteric hepatitis in which 57 per cent of the cases inoculated from a single batch of serum developed icterus after an incubation period of 45 to 90 days. The amount of homologous serum administered at one time varied from 0.1 c.c. to 1,200 c.c., and a study of the

cases revealed that the severity of the disease bore no relationship to the amount of serum given, nor to the route of administration; provided it was given by the parenteral route, intradermal injections were as effective as intravenous or subcutaneous injections. A possible explanation of this inconsistency in dosage is that all but 4 of the subjects studied had been previously treated with injections for allergies.

Homologous Serum Jaundice Following Blood Transfusion

The incidence of transmission of hepatitis by transfusion with pooled serum has been estimated to be 7 per cent.

Transmission by means of whole blood has been shown statistically to be much less. This is explained by the fact that with pooled serum there are many contributors. With serum from many individuals, the chances of infection are very much higher than is the case where a single donor is used in whole blood transfusion. Whereas one batch of pooled serum can infect a large number of persons, with blood transfusion only one person can be infected. The conclusion is that the use of pooled serum or plasma should be avoided altogether until a safe method of sterilization is discovered. Furthermore, only small batches should be used for the preparation of blood products.

Clinical Data

Incubation Period:—The average incubation period in serum-hepatitis is 60 to 120 days. In 405 cases observed by J. M. Hayman and W. A. Read[73], the average incubation period was 100 days with a maximum of 210 days. In Turner's series of 4,083 cases symptoms developed during the fourth month. Most observers report similar figures.

Immunity:—Seven patients in a series reported by J. M. Hayman had had "catarrhal jaundice" previously, and one patient had had an attack of serum hepatitis following yellow fever vaccination three years earlier, after an incubation period of three months.

Prodromal Symptoms:—These are much less pronounced than in epidemic hepatitis, and in many instances are entirely absent. Symptoms of upper respiratory tract infection, which so frequently mark the beginning of infective hepatitis, are rarely observed. This conforms to observations that infective agents are not present in the nose and throat and that there is no contact infection. Darkening of the urine and onset of jaundice are frequently the first symptoms, and among the most commonly mentioned general symptoms are anorexia, weakness, nausea and vomiting, and pain in the right upper quadrant of the abdomen. Burning of the eyes, lassitude, headache and general sweating are frequently observed. The latter may be due to hepatic hypoglycemia. Severe night sweats were prevented by Turner by the administration of drinks rich in carbohydrate late in the evening. Skin symptoms, chiefly in the form of urticaria, were observed in 25 per cent of cases, according to Hayman.

The following table gives a survey of the symptomatology as reported by the British Ministry of Health in 1944:

TABLE I

SIGNS AND SYMPTOMS IN 48 CASES OF SERUM HEPATITIS

Symptoms Recorded	Percentage Incidence of Symptoms
Skin rashes	41.7
Anorexia	85.4
Abdominal pain	25.0
Indigestion	61.4
Change of bowel habits	31.2
Fatigue or sleeplessness	66.7
Dark urine	97.9
Stiffness of joints	25.0
Headache	25.0
Jaundice: Slight	35.4
Moderate	45.8 to 100
Severe	18.7
Rash	19.1
Conjunctivitis	65.9
Petechiae, hemorrhages, etc.	14.6
Liver enlarged	66.7
Liver tender	44.7
Spleen palpable	37.5
Spleen tender	19.1
Lymphadenopathy	17.0
Urine: Bile	100.0
Albumin	52.4
Casts	17.0

On the whole, the clinical symptoms fall in line with those observed in genuine epidemic hepatitis. They are, however, more severe and the mortality is higher. An epidemic observed by Turner was characterized by the early appearance of severe hemorrhages and ascites on the seventh day after onset.

Severe hemorrhages into the intestinal tract and abdominal cavity have resulted in early death of some patients. Attacks of severe pain in the lower abdomen, sometimes suggesting attacks of acute appendicitis, were, as mentioned, explained at postmortem as being due to mesenteric hemorrhages. Bleeding of the gums may become very serious at the height of the illness. The gums may become inflamed, bleed easily and become hypertrophied. Fatal bleeding from varicose veins of the esophagus has been reported after an illness of only a few weeks (Turner).

Ascites:—Turner observed ascites in 13 patients in his series. He believes that capillary injury is responsible for this incident. The condition was observed as early as the seventh day after onset of the disease, in one case on the seventeenth day, and in another, on the seventy-fifth day of the illness. It may subside spontaneously as the general condition improves. In some patients with ascites the history revealed previous liver damage, e.g., malaria.

It is remarkable that damage and destruction in the portal vein system can develop in a short time. Ascites may form in enormous quantities, up to 10 or 20 liters. In spite of the serious signs of portal obstruction leading to rapid develop-

ment of ascites and varicose veins, the damage to the vascular framework may be quickly repaired by complete structural regeneration.

Neurocerebral Symptoms:—Nervous symptoms, fatigue, depression, irritability and restlessness, violent intractability and even convulsions are more frequently observed than in epidemic hepatitis. The clinical picture thus approaches more nearly the syndrome of acute yellow atrophy than that of the common and benign forms of epidemic jaundice. This points to a more pronounced neurotropic activity of the virus strains.

Death Rate:—The mortality has been estimated by Fox[74] as between 2 and 2.5 per cent. Turner recorded 14 deaths in a series of 4,083 cases. The cause of death is either acute atrophy of the liver or fatal hemorrhage into the intestinal tract or from varicose esophageal veins.

The Problem of the Second Factor

The sensitizer or fertilizer:—Anatomy and bacteriology alone do not cover and cannot explain the whole pathological aspect of hepatitis. There are some more general biological problems involved. Research workers in experimental medicine have been almost unanimous in their opinion that there must be at least two factors in producing an inflammatory process in the liver. Bacterial invasion and some sort of toxic agent must cooperate in causing the liver injury. There must be a "seed", a "soil", and a "fertilizer" (Hampson[1]). The seed may be an infection; but in order for the seed to grow, the soil must be prepared by a "fertilizer", i.e. any kind of cell damage. The importance of such a second toxic factor in activating the pathogenicity (virulence) of the infecting virus, or in sensitizing the organ to be invaded, has been stressed by many authors independently (J. P. Fox et al[2], Theiler[3]). Apart from the difference in the infecting virus-strains, the presence and action of sensitizers may well account for the difference in the clinical pictures, such as incubation period, the syndromes of the prodromal stage, and the course of the disease. Some sensitizers are well-known, and their effect in causing primary, though often latent, liver cell damage is fairly well established.

Alcohol:—The damaging effect of alcohol on the liver in causing fatty degeneration and as a predisposing factor in the development of cirrhosis is well known. However, experimental medicine, in trying to reproduce such pathologic changes in animals, could only reach the conclusion that alcohol acts as a pacemaker for a second damaging factor. The effect of alcohol on epidemic hepatitis could be well studied during the last war. The following facts were established:

1) Alcoholic excess may cause a relapse a considerable time after complete clinical recovery.

2) Alcohol may shorten the incubation period from the usual time of 20 to 23 days to 3 to 5 days.

3) Alcohol may provoke an attack of acute hepatitis in a virus carrier.

Relapses with a new outbreak of jaundice following alcoholic excess were observed as late as 2-3 months after complete recovery. In small doses, the effect is doubtful, but there remains the possibility of a cumulative effect (Damodoran

and Hartfall[4]). Repeated relapses owing to errors in diet may drag on for long periods. A case was observed in which such a relapse occurred four times in five years. The influence of alcohol in shortening the incubation period in persons who had been in contact with patients suffering from infective hepatitis, is a remarkable observation which has been recorded by several authors. In one case, the time of the only possible contact could be clearly determined and the shortening of the incubation period from 22-23 days to 8 days owing to alcoholic excess could be demonstrated as in an experiment (Pribram[5]). Most persons who come in contact with infected cases during an epidemic of hepatitis, are potential carriers, though only a small percentage will be taken ill. The question thus arises as to the relation of individual sensitization to the incidence of actual morbidity.

Syphilis and antisyphilitic treatment:—This factor has been referred to in connection with icteric hepatitis for the last fifty years. Antisyphilitic treatment, as an additional liver damage, has proved to have considerable bearing on the incidence of epidemic hepatitis. Special study has been directed to this aspect by G. H. Stokes[6], Ruge[7], Lindstedt[8], Herxheimer and others[9]. The general impression prevails that antisyphilitic treatments, not only with arsphenamines, but also with mercury products, favor the development of epidemic jaundice. The striking figures of Lindstedt are worth mentioning: Out of 101 patients treated for epidemic jaundice, 21 had undergone antisyphilitic treatment with mercury.

Malarial infection:—This disease, too, seems to have been proved to have a sensitizing influence on the liver. Changes in this organ similar to those observed in hepatitis have been described in fatal cases of malaria and have been noted by many pathologists. Jaundice has also been observed during the treatment of malaria. In cases of therapeutic malaria, the cephalin-flocculation tests sometimes became strongly positive.

Liver Extract Injections:—Ottenberg and Spiegel[10] reported 12 cases of mild jaundice during treatment with parenteral liver injections. Liver function tests indicated some impairment. There are cases reported, and the author has seen two, in which a real anaphylactic shock has been observed after liver injections. However, even when no clinical signs appear, the liver damage may be just enough to render the organ sensitized to further damage.

Misuse of Sulfonamides:—It has become almost a habit to take sulfonamides for any one of a number of conditions, such as an approaching cold, sore throat, a slight cystitis, a boil or a whitlow, just as one takes aspirin tablets or vitamins. The soldiers, in all countries, were often provided with sulfonamide tablets in their first aid kits. All sulfonamides are toxic to the liver and to all hematopoietic organs. Recently, we have seen an increasing number of cases of hepatitis with liver edema, and even cases of jaundice caused by these drugs. Agranulocytosis and leucopenia are other well-known results of sulfonamide medication. There is no doubt that even if not taken in excessive doses, their use over a long period may have a damaging effect on the liver and under certain circumstances just sufficiently to sensitize the organ to further infective invasion.

Vaccination:—We cannot close our eyes to the fact that the large-scale vaccinations of soldiers and civilians during the war were not absolutely innocuous, and furthermore that an accumulation of them might well be responsible for a sensitization of the liver. Cases of postvaccination jaundice have been reported (Eppinger[11]) in patients who apparently had suffered from a latent hepatitis, or were virus carriers. The writer observed recurrent attacks of epidemic hepatitis after a typhoid and after a small-pox vaccination. The possibility of a sensitization by means of vaccines in serum hepatitis deserves attention and study.

Fatty Food:—Intolerance to fat is a more or less constant feature in hepatic insufficiency. A fatty meal consumed by a patient with a definite intolerance or allergy, may account for a relapse of hepatitis long after recovery, or for an early outbreak of the disease while the patient is still within the incubation period.

Hypoproteinemia:—Experiments by Miller, Whipple et al[12], established evidence that a low protein diet predisposes to any kind of toxic liver damage. Transmission experiments in virus hepatitis have led to similar observations.

Pregnancy:—Conclusive evidence has been presented that during pregnancy, the liver is in a state of latent damage, a fact which has led to the conception of the "pregnancy liver". On the other hand, the importance of pregnancy in the development of fulminating acute hepatitis leading to yellow atrophy has been recognized. Of 29 cases of acute yellow atrophy in patients from 20 to 29 years of age, observed by Cockayne[13], *twelve* were pregnant women. The first sign of liver damage, observed as a rule between the third and fifth months of pregnancy, is a temporary enlargement of the liver during digestion, a certain "weakness" of this organ during the time of functional strain. It is similar to the "fleeting allergic edema". A slight increase in the urobilin of the urine may be observed at this time. Some liver function tests may become positive.

Psychosomatic factors:—Insufficient attention has thus far been paid to these factors. Lack of appetite and being "fed up" with monotonous food, and especially as regards canned foods, may lead to disgust and repulsion, and greatly interfere with the normal secretion of digestive juices and bile. This, in turn, might lead to incompletely or abnormally decomposed metabolic products, which could have some toxic effect on the liver. It has been well-known since olden times that anxiety and mental excitement may interfere with proper bile secretion, some emotional crises even leading to a *complete secretory block* and the appearance of jaundice, (*icterus ex emotione*).

The conception that a sensitization of the liver is produced by one injury, thus paving the way for secondary damage, is not at all new, and it is rather surprising that such important facts have not been given the consideration they certainly deserve in the textbooks. The importance of a cumulation of damage in the pathology of the liver was already mentioned by Claude Bernard.

It has been known for a long time that chloroform anesthesia repeated within a short time is more dangerous and more likely to cause liver death, than the use of a similar amount of the anesthetic in a single application. The literature on

experimental medicine is full of observations proving that the repeated application of any toxic or infective agent to the liver at intervals, or of different toxic agents simultaneously, will cause more damage to the liver than any single toxic product even in higher doses applied only once. Fiessinger[14] speaks of a "cataphylaxis" of the liver—a term meaning that the resistance of the liver is diminished. He presents a clinical review of interesting cases with hepatitis relapsing after recovery, which well illustrates these facts.

The most common instance is the cooperation between small doses of a toxic product and a bacterial infection, each of which separately—even in higher doses—would cause no damage to the liver at all. In many cases a similarity to allergic reaction may be observed, recalling the interesting experiments on autosensitization of the liver, due to absorption of autolytic liver products and other liver injections. It is conceivable that such a process of autosensitization might take place following liver damage, so that upon later infliction of a second damage, the liver is found already sensitized. It certainly does not follow the simple pattern of a reaction in which the same injury is inflicted twice. It is a nonspecific sensitization of the organ. Fiessinger expresses the facts as follows: "It is the first damage which interferes with the second defense."

Allergic conditions in the initial stages of infective hepatitis are very common indeed. In a case of mussel poisoning reported by Fiessinger, a general urticaria preceded the symptoms of typical infective hepatitis, and in another case cited by Caroli[15], an allergic erythroderma vesiculosum preceded the jaundice. Late reported experiments wtih biological cutireactions on patients who fell victims to hepatitis following antisyphilitic treatment.

Quite frequently the toxic sensitization dominates the initial stage of the disease to such an extent, that some doubts are justified as to whether the disease is caused by infective germs at all, or is of a purely toxic origin. In some instances, this aspect is most striking, as in the formerly so-called catarrhal jaundice. The strongest argument presented by supporters of the toxic etiology of this form of hepatitis is the almost complete lack of an incubation period; the fact that gastrointestinal symptoms appear sometimes as early as a few hours following the ingestion of a suspected meal, is certainly more characteristic of intoxication than of infection. However, bearing in mind what has been said above about the process of sensitization or fertilization, it is possible to view this problem from another angle, which we believe gives the clue to a solution. The clinical signs in this disease actually present the overlapping syndromes of *two* damaging factors. Within a few hours after the ingestion of the noxious meal, the patient feels the first symptoms of an allergic enlargement of the liver as an epigastric pressure, accompanied by anorexia, nausea and a furred tongue. The viruses causing infective hepatitis are ubiquitous. They may have a varying virulence, at times so low that they may be considered as mere saprophytes, with only potential pathogenic properties. This is the case when a healthy carrier, as a blood donor, transmits the viruses of infective hepatitis to susceptible persons. Supposing a person taken ill with acute indigestion is a virus carrier, or is exposed to virus infection,

then all conditions are present which would favor the settling and spreading of hepatotrope viruses in the already damaged liver.

The comparison with another virus infection—the common cold—would not seem out of place for an illustration. Upon returning home following exposure to cold weather, a person may, within an hour, feel all the symptoms of an approaching infection, with edematous swelling of the mucous membrane of the nose, dripping of edematous fluid from the nose, a sore throat and the like. However, these are not the prodromal signs of acute infection. They are actually the signs of sensitization. Exposure to cold causes contraction of the capillaries, anoxemia, damage to the capillary walls in the form of increased permeability, and effusion of fluid leading to perivascular edema. Whereas the intact mucosa forms a fairly safe wall of defense against any invasion of infecting germs, these changes provide favorable conditions for spreading of the everpresent infecting germs, which moreover gain in virulence upon reaching a new medium. In both instances, namely, in the common cold and catarrhal jaundice, the very first clinical signs are those of sensitization. In one phase they may pass into the syndromes of a fully developed infection. This conception well explains the allergic and individual character of these cases and the fact that the same food may cause an attack of acute infective hepatitis, giving the impression of being of toxic origin in one person, and leave others undamaged in full health.

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DISCOVERY OF THE CAUSE AND CURE OF GASTROINTESTINAL ULCERS*

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Since the two major problems in gastrointestinal ulcers are the unknown cause and unknown cure, the work herein presented is a brief statement of the experiences and observations on these subjects during the last thirty years. As the diagnosis of alimentary tract ulcers presents no difficulty it will not be discussed here.

On taking the histories of a number of patients with gastrointestinal ulcer it becomes evident that few remain with one physician in this lifelong sickness. With some variations these patients complain of heartburn, eructation, acid regurgitation, abdominal distention, epigastric pain often disturbing sleep, constipation alternating with diarrhea, occasional vomiting, and dizziness followed by tarry stools.

Continuing the history the patient would begin with one physician who investigated, diagnosed and treated him for gastric or duodenal ulcer five years with regressions, remissions and recurrence of symptoms. Then he shifted to another physician who treated him three years in the same manner with the same result. A third had him three weeks at the hospital with stomach tubes. Now he either was advised operation or he became discouraged and decided to change to a new physician.

This physician may depend on the others for diagnosis or he may reinvestigate him and confirm it. If he treats him with the same standard light, bland diet of milk, cream, cheese, soup, tea, toast, crackers, aided by alkalis and aperients he could not expect to attain any different results than the previous physicians. The patient improves slowly, loses most complaints, has some regressions or even remissions, and though continuing to adhere to the recommended diet and medication, the original complaints suddenly recur.

The question arises why did the patient improve and why under the same standard regimen did he become ill again?

Quite far back, the answer to this question seemed most important, realizing that by using the current conception and management the patient would attain the same, unsatisfactory results. The only difference would be that another physician would be added to his list.

Experimenting years ago in devious ways for long periods yielded evidence that ulcers had nothing to do with the suggested causes of eating heavy, light, or bland food, too much eating, rapid eating, insufficient chewing, irregular eating, regularity of bowels, worry or nervous strain, infection, lack of some hormone, too much acid, or any other supposed cause named up to now. Further investigation proved that food allergy was the only cause of gastrointestinal ulcer. The

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objection to this discovery at that time was that it took months before a patient could be made well for good. The reason being that every patient had to be tested for each food individually. Skin tests and current elimination diet lists had no value. But after accumulating a large number of such individual diet lists, it was possible to extract enough foods to which no one was allergic. This list of foods was found to be ample, it could maintain a person in good health for life, and not a single ulcer patient was found to be allergic to it. It is designated as the primary anallergic foods and is given to the patient as soon as a diagnosis of gastric or intestinal ulcer is made. No medication is given and no alteration in his daily conduct relating to nervous or mental strain is instituted. Only strenuous physical exertion is prohibited. Within a week he is usually free from all distress.

ANALLERGIC FOODS (PRIMARY)

Wheatena, with butter	Meat, boiled or broiled
Farina, with butter	Lettuce
Rice, with butter	Tomatoes
Noodles, with butter	Green peas, boiled
Potatoes, with butter	String beans, boiled
White bread, not toasted	Butter
Eggs, medium or hard boiled	Salt
Fish, boiled or broiled	Seltzer
Chicken, boiled or broiled	Water

The patient is kept on these foods about a month during which time his allergic sensitiveness is found to decrease. Now he is given a second list designated, the extended anallergic foods, embodying the primary anallergic foods, to which he adheres another month. The patient's attention is called to the fact that there are enough foods on this list to maintain him in good health for life.

ANALLERGIC FOODS (EXTENDED)

Eggs, medium or hard boiled	Wheatena, with butter
Fish, boiled or broiled	Farina, with butter
Chicken, boiled or broiled	Rice, with butter
Duck, boiled or broiled	Noodles, with butter
Goose, boiled or broiled	Spaghetti, with butter
Beef, boiled or broiled	Potatoes, with butter
Veal, boiled or broiled	Lettuce
Lamb, boiled or broiled	Tomatoes
Ham, boiled or broiled	Celery
Pork, boiled or broiled	Green peas, boiled
Oysters, raw	String beans, boiled
Clams	Beets, boiled
Shrimps, boiled	Carrots, boiled
Butter	Cauliflower, boiled
Chicken fat	Seltzer
White bread, not toasted	Water

The patient is kept on this diet a month. At the end of the second month of his treatment, the patient has lost much of his allergic sensitiveness, he is feeling well and is asking for more foods. Now he is given a third list called the semi-allergic foods of which he is permitted to *try* small amounts infrequently. Should he experience any distress he is instructed to return to the primary anallergic foods for about a week and then to the extended anallergic foods for about a week or two, and then he may again try some of the semiallergic foods, as his allergic sensitiveness might have further decreased. In reality an ulcer of the gastroin-

testinal area is not as mysterious as the prevailing conception seems to indicate. It is the old familiar eczematous ulcer on the mucous membrane instead of skin, in this case due to food allergy.

The semiallergic foods which may be *tried* after the patient has been symptomless a month on the extended anallergic foods are:

SEMIALLERGIC FOODS

Corned beef	Jello
Tongue	Pears, raw
Lobsters, boiled	Peaches, raw
Chow mein	Plums, raw
Roast beef, without gravy	Cherries, raw
Salmon, canned	Bananas
Liver, boiled or broiled	Watermelon
Brownies	Cantaloupe
Honey buns	Honeydew melon
Apple juice	Stewed prunes, without juice
Cocoa, prepared	Applesauce, without sugar
Sweet cream, heavy	Buckwheat groats, with butter

Thus the patient is treated by removing the cause and not only empirically by ameliorating his ill effects and allaying his suffering. No medication of any kind is used in this treatment and the patient remains permanently well.

Since many patients still keep asking for various foods, a fourth list, called allergic foods, definitely prohibited, is given them which eliminates many questions.

ALLERGIC FOODS (MUST NOT TAKE)

Hot water	Jelly	Figs
Tea	Cheese	Dates
Coffee	Crackers	Raisins
Milk	Zweiback	Herring
Malted milk	Toast	Anything fried
Sour milk	Rye bread	Anything stewed
Sour cream	Wholewheat	Sauces
Soup	Bran	Gravies
Beef juice	Dry cereals	Catsup
Prune juice	Mushrooms	Pepper
Liquors	Sweet potatoes	Onions
Syrup	Dried or baked beans	Radishes
Sugar	Spinach	Horseradish
Candy	Apples—raw or baked	Pimiento
Ice cream	Oranges	Spices
Cake	Grapes	Stomachics
Pie	Grapefruit	Appetizers
Pudding	Strawberries	Condiments

At this stage no one could quarrel with any physician who wants to check and recheck in any manner he desires to find whether the ulcer healed. However, the experience gained in hundreds of cases in the last twenty-five years proved that the loss of all complaints by the patient is the best evidence. Therefore, no x-ray films of "before and after" are here presented. These have been so often shown with the standard management that nothing would be gained by this kind of demonstration. The only difference is that in the standard treatment the patient's symptoms return while with this treatment they never return.

Let it be recalled that allergy is an abnormality arising in about five to fifteen persons out of every hundred who ingest, inhale or otherwise come in contact

with certain substances. The best conception of allergy in relation to the subject under discussion could be gained by citing the following three criteria postulated by Duke:

First:—If the allergic substances are prevented from coming in contact with the sufferer the abnormalities cease, as it occurs when the allergic foods are withheld from the ulcer patient and he is made to subsist on the anallergic foods.

Second:—If the allergic substances are again permitted to come in contact with the sufferer then his previous abnormalities return, as when the ulcer patient disregards the anallergic foods and returns to his previous allergic diet.

Third:—If the suffering person persists in taking the allergic substances, then the tissues develop an immunity for various periods of time and the abnormalities disappear for that interval.

Thus is explained the phenomenon of an ulcer patient improving under one treatment or another or under no treatment, but his symptoms reappear when his allergic sensitiveness returns. In order to remain symptomless for life he would have to adhere to the anallergic foods or return to them as soon as symptoms appear. This is the only cure any allergic patient can be promised. No medication is needed or given. The patient could only be made worse as he was found to be allergic to all medication used in the standard management of ulcer, whether antacids, laxatives or antispasmodics. It also becomes evident how futile it is to expect a surgical cure for gastrointestinal ulcers. There are over twenty feet of the tract and no matter what part is excised there remains enough mucous membrane for a new lesion to develop. The fact that some patients are more sensitive in one area than another does not alter the situation, because when the most sensitive area is removed an adjacent part becomes sensitive. Surgery is only indicated in complications of ulcer, pyloric obstruction, adhesions to the pancreas, or perforation.

It also becomes evident that as soon as we have to look for food allergy as the cause of gastric or intestinal ulcers, then the repeated stomach and bowel contents examinations—whether fasting or after meals or fractional—or bacteriological examinations could not reveal the cause of the malady. These examinations could not reveal the cause of gastrointestinal ulcers any more than investigating the size, shape, secretion, and bacterial flora of the respiratory tract would lead to the discovery of the cause of hay fever or asthma. The proof lies in making the patients sick by having them inhale or ingest these substances, and keeping them well as long as these allergic substances are withheld. In gastrointestinal ulcers the ingestion of allergic foods is the causative factor. The cure is the anallergic diet.

One more illustration will help to clarify our contention. The remarkable thing, for instance, about the standard treatment, which is based upon "light" foods, is that all gastrointestinal ulcer patients are allergic to all foods and most medication recommended. The reasons for the popularity of milk, as an example, are two. First, it is considered such a "light" food that even new-born babies can digest it. The fact that many babies get colic, vomiting spells and diarrhea because they are allergic to milk is completely ignored. Second, it allays pain in an

ulcer patient for a few hours. It is true that the milk as it comes into the stomach is antiallergic and thereby stops the pain, but its cleavage products are strongly allergic substances. Therefore, the patient has to drink the milk at frequent intervals, not because the milk left the stomach but because its cleavage products appeared and caused distress. The absence of an ulcer with the same complaints simply indicates a flat or urticarial rash instead of a dugout or ulcerous rash. Both clear up with the above anallergic diet.

To demonstrate the working of this method more clearly the following are reports of a few gastrointestinal ulcer patients treated unsuccessfully for various periods in the prevailing manner, then by the method here presented. Most of them had heartburn, eructation, acid regurgitation, vomiting, epigastric pain disturbing sleep, constipation alternating with diarrhea. Some had fainting spells followed by vomiting blood and bloody stools.

Case 1:—J. K. Between 1925 and 1944, this patient had all the above symptoms, with regressions and exacerbations, including night pains and fainting spells followed by bloody stools. During these nineteen years he had been diagnosed and treated as a duodenal ulcer case by various physicians at their office, at his home in bed, and many weeks in the private pavilion of a large New York hospital. In accordance with the standard conception he was put on a light bland diet of milk, cream, alkalis, aperients, and the rest that goes with it, but to no avail. He continued to have recurrences, regressions and exacerbations.

In 1944, reinvestigation confirmed the diagnosis of duodenal ulcer. He was put on the anallergic diet. In a short time he lost all his complaints and has been well ever since then. If he digresses from the diet and begins to get some ulcer symptoms then he reverts to the anallergic diet and is well again. This is the only treatment which kept this ulcer patient continuously well. No medication. No recurrences as long as he adheres to the anallergic diet.

Case 2:—I. L. This patient's suffering began in 1939, with heartburn, epigastric pain disturbing sleep, considerable eructation and abdominal distention. In 1943, she had vomited blood and passed bloody stools. Investigation at that time revealed a bleeding ulcer. She was kept in bed six weeks and given the standard ulcer treatment of milk, alkalis and the rest that goes with it. The bleeding ceased but the gastric distress continued for another three years, in spite of scrupulously adhering to the ulcer treatment. On January 1, 1946, she had another gastric hemorrhage and three weeks later she came to the office.

Investigation on January 24, 1946, revealed a duodenal ulcer. She was put on the anallergic diet and she has been well ever since then. No medication. No recurrence.

Case 3:—M. C. For years this patient had heartburn, eructation, burning pain in epigastrium extending up to the chest and down to the umbilicus. He had occasional bleeding from the ulcer with the passage of tarry stools. At those periods he felt dizzy and had shortness of breath. This patient was given the standard treatment for peptic ulcer with the usual regressions, remissions and recurrences.

In 1946, reinvestigation corroborated the diagnosis of duodenal ulcer. He has been on the anallergic diet and is continuously well. No medication. No recurrences.

Case 4:—W. M. For years this patient had suffered from heartburn extending to the throat and the back, disturbing sleep. He had been diagnosed as a duodenal ulcer case and given the standard treatment of milk and alkalis, to no avail. He was finally advised to go to a well recognized clinic in Boston where he was investigated and told that he was suffering from a penetrating duodenal ulcer and would most likely have to be operated on.

In August 1947, the patient was again investigated and found to suffer from a duodenal ulcer. He was put on the anallergic diet and has been well since then. If he digresses from the diet for long he begins to have a return of his ulcer symptoms. All he has to do is to resume the anallergic diet and he is well again. No medication. No recurrence.

Case 5:—S. A. In 1943, this patient began with severe epigastric pain disturbing sleep. For two years she had been treated for duodenal ulcer in the prevailing manner with regressions and exacerbations of her pain.

In 1945, investigation again revealed a duodenal ulcer. Since then she has been on the anallergic diet and has remained continuously well. She occasionally tries foods recommended in the standard diet but soon her symptoms begin to return and she must resume the anallergic foods to continue free from symptoms. No medication.

Conclusion:—The cause of gastrointestinal ulcer is food allergy and the cure is the anallergic foods.

It will be noticed that in the histories the age and the marital status were omitted because they are of no significance. While most patients are between twenty and forty years of age, the youngest observed was four and a half, the oldest seventy. Occupations requiring physical exertion, lifting, pulling, pushing, carrying heavy objects, the same as physical exercise are contraindicated. All other occupations have no bearing on this disease.

I tried to avoid theories and to present the facts gathered from the last twenty-five years of experience with this method on hundreds of gastrointestinal ulcer patients. My most earnest wish is that physicians try it and report on it. Arguing that it sounds too simple or fantastic helps no more than maintain that diphtheria antitoxin, the sulfonamides or antibiotics do not work without trying them. You can only judge the value of this method after trying it. There is enough information of the exact use of this method in the literature as noted in the bibliography.

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SYPHILIS OF THE RECTUM*†

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Syphilis of the rectum is said to be infrequent, and cases of primary rectal syphilis are rarely observed. However, this may be due not to their infrequency but rather to the fact that many such patients are self-treated under the impression that the condition is simply a mild attack of hemorrhoids. Pain is usually slight, and the primary condition may heal spontaneously, or the patient may later receive antiluetic treatment when a secondary rash has appeared, the rectal lesions being entirely overlooked. Even the more obvious syphilitic manifestations such as condylomata lata need to be distinguished diagnostically and therapeutically from the nonluetic condylomata acuminata. Syphilis, in the rectum, earns its cognomen of "the Great Imitator", and may remain undiagnosed because of a resemblance to more usual rectal conditions.

Two cases are presented in which the diagnosis of syphilis was made in conditions which masked themselves as common anorectal disease.

1. *Syphilis simulating fissure-in-ano:*—J. B., male, colored, 16 years old, a schoolboy, complained of anal pain of two weeks duration, with traces of blood on defecation. The pain was typical of fissure, i.e., sharp, cutting and lasting several hours after bowel movement. Examination revealed a deep fissure, with indurated edges, in the right posterolateral anal quadrant. The sphincter was spastic. There was nothing specifically to arouse suspicion that we were dealing with anything other than an ordinary fissure-in-ano, except for two factors, both capable of easily being overlooked: first, the presence of indurated walls in a fissure of such recent origin; second, the presence of a single tiny, grayish maculopapule, less than one-half centimeter in diameter, on the buttock, near the intergluteal fold. This was identified as a lesion of the secondary stage of syphilis. Examination of the skin of the body, hands and face then revealed one other insignificant lesion at the angle of the mouth. A blood Wassermann and a darkfield examination of material from the fissure were both positive. With the first injection of neoarsphenamine the fissure and other lesions began to heal, and disappeared entirely with the third treatment, after which he was referred for complete antiluetic therapy. No local treatment was employed. Sodomy was repeatedly denied.

The indices of suspicion of syphilis in this case were an indurated recent ulceration with a surrounding inflammatory reaction, and the single maculopapule, which could easily have been overlooked.

2. *Syphilis simulating rectal carcinoma:*—S. G., male, white, age 46, complained of diarrhea alternating with constipation of one week duration. He had previously been constipated. He was now passing liquid stools with small amounts

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of blood. His appetite was poor, he had lost a moderate amount of weight, and felt weak. He had been told by a physician that he probably had a rectal tumor.

Digital examination was painful and showed large smooth lobulated masses filling the lower rectum so that the index finger could not enter completely. Proctoscopy, employing a tube of small diameter, revealed smooth, hard protrusions of the rectal walls into the rectal ampulla, almost obliterating it. The mucosa showed some abrasions but was not ulcerated. A biopsy of these masses was reported by the pathologist as inflammatory tissue, but the swellings so resembled a neoplasm that the biopsy was repeated, with the same result. A Frei-test was performed with negative results. A Wassermann test was then done and reported as 4 plus. When the patient was informed of this and questioned further, he admitted sexual contact per rectum about three or four weeks before the initial symptoms.

It is generally considered that if the biopsy report is negative in a case of clinically diagnosed carcinoma, the laboratory findings should be subordinated to the clinical findings. In the present case this rule did not hold. In retrospect, the factor which led to hesitation in accepting the diagnosis of malignancy was the smoothness and lack of ulceration in the lobulated mass. A rectal neoplasm of this size would, as a rule, be expected to have ulcerated. In fact, some ulcerations did begin to develop a few days later, and had it been seen first then, the signs would have been more misleading. As it was, this very rapid change in appearance, within a few days, acted as an additional differential sign, such rapid changes not being characteristic of the usually slow-growing rectal malignancies.

With administrations of intravenous arsenicals the rectal masses rapidly subsided and the patient announced, a few days after the very first treatment, that he felt much better, was moving his bowels more normally and that the diarrhea was subsiding. Subsequently, the masses disappeared completely.

The pathology in this case was apparently the proctitis of early rectal syphilis, an inflammatory hyperemia and induration, which may become ulcerative, involving the loose submucosal tissues of the rectal wall.

To sum up, the differential diagnosis between syphilitic proctitis and malignancy is aided by noting in syphilitic proctitis (1) the early smooth, nonulcerated appearance; (2) the relatively rapid appearance and increase of symptoms and signs; (3) changes in appearance of the lesions within a short time; (4) negative biopsies and Frei tests; (5) positive Wassermann reactions and dark fields; (6) possible subsequent secondary rash.

Comment

In one of the above cases (that simulating fissure) an error in diagnosis would have resulted in loss of the "golden opportunity" of antiluetic treatment at the early stage when it is most effective. Suspicion of syphilis must be ever-present since even proctologists have occasionally been embarrassed by excising supposed fissures which were in reality chancres, as shown by the pathological report and by the development of secondary lesions shortly after operation.

In the second case (simulating malignancy) an incorrect diagnosis might have meant an abdominoperineal excision of the rectum with a permanent colostomy. If he escaped surgery, in the absence of appropriate treatment, he might very possibly, in view of his severe induration, have developed a syphilitic rectal stricture, although syphilitic strictures are admittedly considered to be the exception rather than the rule.

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ARTHRITIS AS RELATED TO GASTROENTEROLOGY

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Arthritis rarely influences the life span of a patient, however, the disability produced often makes the patient a lonely individual whose socioeconomic conditions are adversely affected. The necessity to curtail activity and the thought that resultant deformities may make the patient dependent are of greater concern than the disease.

In considering the arthritic patients, many physicians fail to see beyond the affected joints. The necessity of a thorough and complete medical history cannot be stressed too strongly. More frequently than not, the patients will reveal that the arthritis syndrome started with some gastrointestinal complaints.

It is not our purpose to present any new or investigational data, but we would like to associate practically the specialties of gastroenterology and rheumatology.

We want to submit that in drawing up a therapeutic regimen for many of the arthritides, the gastrointestinal tract, particularly the colon, must be given serious consideration. Any other procedure may result in failure to the patient.

A brief review and discussion of the varous arthritides related only to gastroenterology should serve more easily to correlate the facts.

1. Degenerative or Osteoarthritis:—(Also known as hypertrophic arthritis and senescent arthritis.)

Degenerative arthritis is present to some degree in all beyond 35 years of age. A symptom syndrome is not manifested unless such factors as trauma, (direct or static), climacteric and emotional instability present themselves. The general health of the patient with this type of arthritis is rarely impaired.

Etiology:—The etiology of degenerative arthritis has not been established. A few of the etiologic considerations are: aging processes (wear and tear), direct joint trauma or injury by static trauma (occupational strain), and obesity. Emotional instability and overeating, which in many instances produces obesity, diabetes and hypertension are accepted initiating factors. In many females the symptoms of osteoarthritis are associated with the menopause, whether natural or artificial[1,2,3]. Obesity produces a combination of direct and static trauma (the excess load carried and parasiting blood supply). Most obese individuals, especially the three "F's" (fair, fat and forty), present definite gastrointestinal symptoms, particularly those associated with gallbladder syndromes. It has been observed that many patients diagnosed as osteoarthritic date their symptoms for many years to muscular rheumatism with a prolonged history of gastrointestinal complaints referred to as bilious spells, sick headaches or "gas indigestion"[4].

We refer to osteoarthritis as a degenerative type, therefore, consideration must be given to the modifications in the physiological factors which take place

in the body and usually result in reduced metabolism. This dysfunction is known to be deleterious and tends to accelerate degeneration in the tissues[5]. The following is a brief picture of a patient complaining of degenerative joint disease.

The joints most commonly affected are the ends of the fingers, hips, spine and knees. The fingers and knees are sites producing most complaints. This should be obvious, as the greatest amount of wear and tear is placed upon these structures (the fingers for delicate and forceful use; the knees for carrying the load, especially in an overweight patient). There is degeneration of the joint cartilage with later involvement of the bone at the joint margins (Heberden's nodes). Stiffness and soreness are the outstanding complaints. In uncomplicated degenerative disease the patient is comfortable when inactive.

2. Rheumatoid Arthritis:—(Also referred to as atrophic arthritis, proliferative arthritis and infectious arthritis.)

Into this category may be placed Still's disease (juvenile arthritis) and Marie-Strumpell disease (rheumatoid spondylitis).

Etiology:—The etiology of rheumatoid arthritis has not been established and still remains controversial. Such findings as increased sedimentation rate, leucocytosis (in acute forms) and the accompanying inflammation of synovial membrane and periarticular tissues strongly suggest an infective basis.

The concept of focal infection has been integrated into the practice of medicine. One speaks no longer of the theory of focal infection. It is recognized as a definite pathologic condition requiring scientific diagnosis and treatment[6].

It has been suggested[7] that focal infection in the colon is a common and important factor in rheumatoid arthritis. In recent years more and more importance is being attached to the colon as a possible factor in the production of arthritis, and the part which the intestinal tract plays as a focus of infection[8].

The lower alimentary tract was regarded[9] as being responsible for more infectious foci than the more frequently incriminated upper respiratory tract in rheumatoid arthritis.

Observations have been reported[10,11] to the effect that the alimentary hyperglycemia reaction is unusually high and prolonged in a large proportion of arthritic patients. It was believed[11] that carbohydrate tolerance was impaired only when there was evidence of infection and inflammation in the alimentary tract.

It has been demonstrated[12] that bacteria, which are not destroyed in the tissues, blood or liver, are dumped into the intestinal tract and the colon becomes the ultimate repository. An abnormal intestinal flora produces stasis with local foci of infection and damage to the mucous membrane.

The incidence of arthritis in patients with ulcerative colitis has been estimated[13] and the relationship is presumed to be the secondary infections which occur so frequently in ulcerative colitis.

In the early stages of arthritis there exists a disturbance in the physiological process which, in all probabilities, is largely of a functional nature. This disturb-

ance permits the deleterious actions of infectious processes to manifest themselves in organic changes. A pathologic trend in the patient's physiological process as a result of the presence of infection is rather difficult to ignore and deny[14].

The role of streptococci, particularly Group A, as etiologic factors in rheumatoid disease, has its proponents and opponents. There are investigators who find that they cannot harmonize the microbic theory of rheumatoid arthritis with modern knowledge. However, it is well established[15-18] that many patients with rheumatoid arthritis, especially those with active progressive disease, possess an antibody in their sera which will agglutinate Group A streptococci. The demonstration of these agglutinins is regarded as strong evidence of activity[15].

The concept, that joints and muscles injured by previous exposure to streptococcal toxins become sensitized before they become susceptible to the toxins arising in a septic focus, is a sound one. The irritant sets up an acute inflammatory reaction localizing it by the development of a lymphatic blockade which tends to wall off the irritant. Once a synovial reaction to a substance arriving by way of the blood stream has become established, it tends to become more intense because a local increase in capillary permeability permits the deposition of still larger amounts of the offending agent[19].

The following is a brief picture of the rheumatoid state: The prodromal signs are weakness of the intrinsic muscles of the feet and hands, accompanied by pain and "pricking" sensations. The disease process of rheumatoid arthritis in most patients may run an active course of some months or even years, then become quiescent. The disease has no specific pattern. An acute type may manifest several acute attacks at intervals of months or years, then assume the characteristics of the chronic progressive type.

Examination of the joint, will reveal characteristics of rheumatoid arthritis. The disease has a particular tendency to attack the small peripheral joints first and most severely. Extreme but irregular muscular weakness may be present. A distinguishing feature of the disease is the symmetrical distribution of the joint involvements, muscle atrophy, spasms and ankylosis. Such findings as loss of weight, loss of appetite, fatigue, high erythrocyte sedimentation rate and anemia are outstanding diagnostically.

Nutrition in Arthritis

1. Degenerative Type:—Nutrition in degenerative arthritis depends upon the presence of overweight, this being as indicated, one of the predisposing traumatic factors. Reduction of the excess weight by a proper dietary regime is essential. This regime must be developed as the result of a careful study of any dyscrasias of the gastrointestinal tract.

2. Rheumatoid arthritis:—A careful review of the patient's dietary history is a requirement. This history will often reveal that although the patient is getting an apparent adequate amount of food, the diet is deficient in the necessary calories and proteins. With an inadequate protein intake, there is a tendency toward lowered resistance, and the delicate balance of infection and immunity is affected.

It has been reported[20] that a high proportion of patients with rheumatoid arthritis in whom liver function was studied showed evidence of liver damage as determined by the Azorubin test. In the presence of hepatic dysfunction, it is obvious that the transfer from a dietary protein to a tissue protein can be greatly interfered with, and the metabolism of vitamins may be abnormal to the point of producing deficiency states.

Abnormal bowel roentgenograms were found[21] in many arthritic patients. The gastrointestinal symptoms were attributed to Vitamin B deficiency. It was suggested[22] that Vitamin B deficiency produced thinning, atrophy and atonia of gastric and intestinal membranes, leading to decreased food absorption with ultimate depletion of body reserves and increased susceptibility to secondary infection, possibly through the abnormal bowel wall.

Increased capillary fragility and permeability occur frequently in rheumatoid arthritis[23]. This phenomenon may be considered a clinical manifestation of the disease. The causative factors may be bacterial toxins or various toxic metabolic products which produce damage in the endothelium of the capillaries. Vitamin C avitaminosis has been suggested as a possible contributing factor, however, it has been demonstrated that a positive reaction to a capillary resistance test does not necessarily denote such an avitaminosis. It has been postulated[24] that hesperidin, a Vitamin P-like substance, is essential to the utilization of Vitamin C for the formation of the cement substance to maintain normal capillary integrity.

Regarding vitamins, it has been established[25] that single vitamin therapy is of limited, if any, value. Single vitamin deficiencies are uncommon; multiple vitamin deficiencies are the rule[26].

Since rheumatoid arthritis has a tendency to become chronic and result in more or less permanent structural and functional changes, the serious nature of the disease from a nutritional standpoint is apparent. The presence of foci of infection in the lower intestinal tract, or possible foci in other parts of the body, plus an aggravated sluggishness of the bowel would obviously permit the accumulation of a greater residue to interfere with the transfer from a dietary to a tissue protein. The ultimate results are muscle atrophy and loss in weight. Furthermore, the autolytic products of traumatized and infected tissues produce destruction of protein so that it cannot be utilized. On this basis the dietary needs of the patient are increased.

3. Specific arthritides accompanying gastrointestinal disease and dietary deficiencies:—

a. Bacillary dysentery has arthritis as an outstanding complication in 3 per cent of cases. This is especially true of the Shiga infections. The arthritis may last from a few days to several months. Complete recovery is present in most every case.

b. Typhoid infections present a definite muscular and joint picture: severe aching, weakness and pain during the febrile stage.

c. Infectious jaundice or Weil's disease presents severe muscular aching and tenderness in the limbs and back.

d. Arthritis associated with scurvy, has as its outstanding manifestations, pains in the legs, occasionally joints of hips, knees and ankles are involved.

e. Pellagra presents muscle cramps and shooting pains in the legs and tenderness over the spine.

f. Beriberi presents muscles sensitive to pressure.

g. Osteomalacia, common in the tropics in pregnancy, presents severe pains in the back, pelvis and legs.

Many of the medicaments used in the treatment of arthritis produce an irritating and sometimes a deleterious effect on the gastrointestinal tract. Unless a history of ingestion of such drugs is obtained, one may be at a loss to eliminate the gastrointestinal disorder. We always make it a point to inquire, "What has your previous treatment consisted of—injections included."

The drugs most commonly involved are:

1. Aspirin:—There is an intolerance to this drug in many arthritic patients. Epigastric distress with its various symptoms is a major complaint. An acute blood dyscrasia may occur in some patients.

2. Cincophen:—Although not used widely today because of its toxicity, it is in sufficient use for one to be on the lookout for its many deleterious effects. It produces gastric irritation in many instances. It has produced occasional fatal hepatitis, specifically an acute yellow atrophy of the liver.

3. Colchicine:—Produces in some instances a burning in the throat and fundus of the stomach, severe tenesmus and diarrhea. The stools become bloody and the syndrome resembles arsenic poisoning or cholera. It must be borne in mind that colchicine given in controlled therapeutic doses produces a mild diarrhea.

4. Vitamin D:—Intoxication as the result of large doses is manifested by the gastrointestinal symptoms of nausea, anorexia and diarrhea. Additional indications may be lassitude, polyuria and impaired kidney function. Unless the dosage of Vitamin D had been very high and taken over a long period of time, the toxic symptoms are usually reversible upon cessation of the drug.

5. Gold salts:—Present many toxic manifestations in the gastrointestinal tract. Stomatitis and acute gastroenteritis are not uncommon. There are occasional cases of hemorrhage in the bowel as the result of purpura, agranulocytosis or an aplastic anemia.

Since the development of BAL many of the serious complications can be controlled. In our experience, however, BAL has not always been successful.

6. Prostigmine methyl sulfate (1:2000 injectible) is sometimes used to relieve muscle spasm. On occasions when more frequent injections than once daily are used, abdominal cramps are the rule. This may be overcome by the use of atropine.

7. X-ray therapy when used to relieve the symptoms of rheumatoid spondylitis ofttimes produces nausea and vomiting when given over the thoracic area.

8. Steroids:—The effects of the newer steroids on the gastrointestinal tract have been observed, however, their true pharmacologic action and toxicology have not been fully determined.

Comment

There is ample evidence to support our suggestion that there is need for close cooperation between the gastroenterologist and rheumatologist. Any approach to the diagnosis and treatment of arthritis which fails to take the gastrointestinal system into consideration will invariably fail to be therapeutically profitable to the patient.

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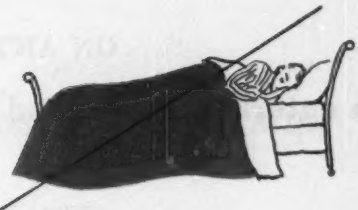

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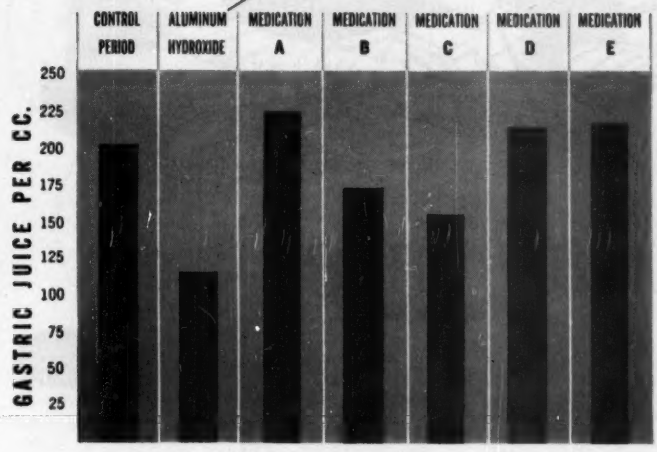

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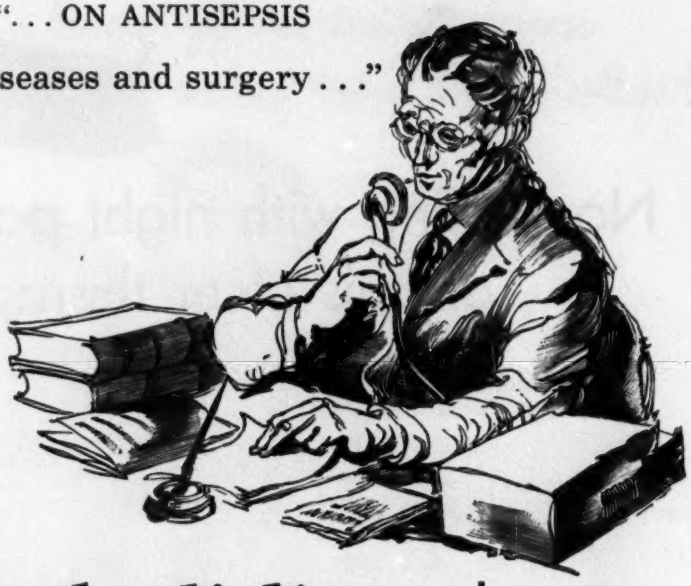

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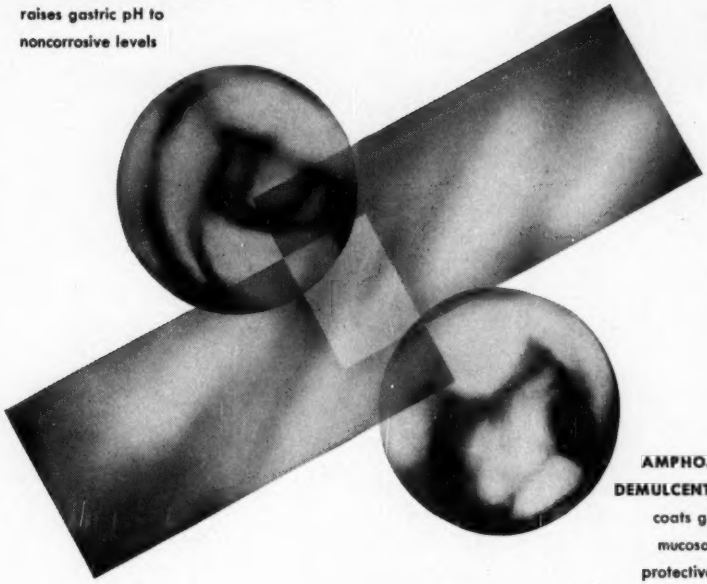

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